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# LECTURES

ON

# AUTO-INTOXICATION IN DISEASE

OR

# SELF-POISONING OF THE INDIVIDUAL

BY

CH. BOUCHARD
PROFESSOR OF PATHOLOGY AND THERAPEUTICS; MEMBER OF THE ACADEMY OF MEDICINE, AND PHYSICIAN TO THE HOSPITALS, PARIS

TRANSLATED, WITH A PREFACE AND NEW CHAPTERS ADDED

BY

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**SECOND REVISED EDITION**

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# PREFACE TO THE SECOND EDITION.

In placing this revised translation of Professor Bouchard's "Lectures on Auto-intoxication in Disease" before my medical brethren, I feel that I am performing a service useful to the profession. No apology is required from me, unless it be for the failures on my part to render fluently into English the meaning of the French text.

For many months now I have been hoping that Professor Bouchard would publish a new edition of this book. The demands upon the time of this distinguished French *savant*, however, have been such that he does not feel equal to rewriting or revising his original lectures at present. This is a loss to medical science we all regret, for auto-intoxication is a subject particularly his own. In giving to the profession a new edition of this work I have tried, fully aware of my many inequalities as a substitute for Professor Bouchard to bring the subject of auto-toxis up to date while yet retaining the rendering of the original translation.

Bouchard deals, in his "Auto-Intoxication," with subjects of everyday interest to the medical practitioner. Many of the facts therein alluded to can no longer be ignored. Putrefactive processes in the intestinal canal and the development of physiological and pathological alkaloids play an important part in many disease processes until lately unknown or misunderstood. These lectures may, therefore, be regarded as an inquiry into the operation of poisons introduced from without or generated within the body of man, and the part they play in health and disease. No subject commands a greater interest; none demands more serious study.

Death frequently carries off in a few hours or days individuals who are in the prime of life and in apparent good health, and at the autopsy the most careful examination fails to reveal alterations of structure such as can explain the fatal stroke.

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Epidemics, not of a specific character, but traceable to poisoned water or food, have unexpectedly appeared in certain neighborhoods; or members of a marriage party have died without much warning, death being attributed, and very properly, to some article of diet partaken of at the wedding feast. These are the cases that have aroused public opinion and awakened professional interest in a subject toward the elucidation of which the pathological chemist has vied with the bacteriologist.

The investigations of Selmi, Brieger, Pasteur, Fränkel, Hankin, Martin, and Bouchard, not to mention others, have shown how disease may depend upon the presence in the system of substances capable of combining with acids to form chemical salts, and which correspond to inorganic and vegetable bases. It was to these substances that the Italian toxicologist, Selmi, gave the name of ptomaines,—by which is meant chemical compounds basic in character, and formed by the action of bacteria upon organic matter. It is in consequence of these basic properties and from their resemblance to vegetable alkaloids that ptomaines are sometimes spoken of as putrefactive or vegetable alkaloids,—the term leucomaines, or animal alkaloids, being reserved for those basic substances resulting from tissue metabolism in the body.

Without discussing the question as to whether ptomaines are poisonous or not,—for Bouchard in these pages confines himself rather to the general action of animal poisons than to a detailed designation of them,—it is sufficient to state that not all ptomaines are poisonous. Some are quite inert. Brieger restricts the term ptomaine to the non-poisonous basic products, while those that are poisonous he calls "toxins." Ptomaines contain nitrogen, and in this respect they resemble vegetable alkaloids. Many of them contain oxygen, while in others this is wanting.

The one invariable circumstance surrounding the development of ptomaines is the part played by bacteria. As ptomaines owe their development to the activity of micro-organisms it must follow that the alkaloid formed will depend upon the peculiar bacterium present, the nature of the material acted upon, the conditions under which putrefaction goes on, and probably, too, upon the health of the individual in whose body the putrefactive processes are taking place. It has frequently been demonstrated how the nature of the soil alters the characters of the micro-organisms that have flourished upon it. Temperature exercises its own peculiar influence. Some bacteria, too, require oxygen, while others are capable of thriving apart from it. Thus it was that Pasteur divided bacteria into two classes: the aërobic and the anaërobic. When putrefaction occurs in the presence of air, the ptomaines formed differ from those produced under conditions from which air is largely excluded. At all times they are extremely subtle. Occurring as transition products in the processes of putrefaction, ptomaines are to be regarded as "temporary forms through which matter passes while it is being transformed by the activity of bacteria from the organic to the inorganic state" (Vaughan and Novy, "Ptomaines and Leucomaines"). The daily round of human life is a repetition of integrations and disintegrations, of processes of building up and breaking down. Metabolism is taking place everywhere within the human body, with the result that the complex molecules of brain and muscle in their catalysis pass through intermediate stages, and are finally resolved into carbonic acid, water, and ammonia. We do not know what part oxygen plays in putrefaction, but the researches of Pasteur have shown how important is the rôle played by micro-organisms. We are forced to acknowledge the great impetus given to disintegrating processes in organic matter by bacteria. In no part of the body is this more true than in the intestine. At the present time it is a debatable question as to how far even normal digestion may not be aided by the functional activity and multiplication of micro-organisms. Pasteur has isolated as many as seventeen microbes from the mouth. Some of these dissolve albumin, gluten, and casein, while others are capable of converting starch into glucose. Considering the multiform changes that take place in the small intestine during digestion,—changes of a chemical, putrefactive, and fermenting nature,—there must be produced substances of a highly complex nature—alkaloids or ptomaines—which, when absorbed into the system, may seriously affect the vitality of the individual. We are all, to some extent, protected against the injurious effects of micro-organisms by the fact that certain products formed within the body as the result of microbial activity react upon the micro-organisms themselves, thus limiting their longevity and diminishing their power for harm.

By this means man is rendered immune, and a defense is raised in the human organism against disease. How far, speaking generally, immunity is brought about by chemical or biological methods it is difficult to say. Herter ("Lectures on Chemical Pathology") deals at considerable length with this important subject. He considers that the chemical defenses of the body are directed mainly against bacteria, bacterial toxins, and poisons other than those toxins formed during digestion, during metabolism, or introduced from without. The acidity of the gastric juice, for example, is a means of defense against certain micro-organisms; so, too, is the acidity of the urine. A much more important defense against microbes is the bactericidal action of the blood and lymph. This, according to Hankin, may depend upon the alkalinity of these fluids, or it may be due to the presence of proteids resembling enzymes derived from the leucocytes. It is common experience that during acute infectious fevers there is developed in the human body substances that destroy bacteria or their toxins. During the early stages of pneumonia, for example, while the specific microbes or pneumococci are multiplying the patient is often extremely ill and yet hardly has the crisis been reached than, notwithstanding the continued presence of these micro-organisms in the body as revealed in the expectoration, or if the case has gone wrong in the discharge from an empyema which has unfortunately formed, the patient feels well and is little disturbed, although pneumococci are still plentiful. This feeling of well-being must depend upon either the pathogenic micro-organisms becoming destroyed by the bacteriolytic action of the blood or upon a neutralization of the products formed by the pneumococci. It would appear that both bacteriolytic and antitoxic effects are capable of being produced. The circulation of toxins in the blood is sooner or later followed by the development of antitoxins. Ehrlich is of the opinion that "toxins unite with the protoplasm of living cells much in the same way as nutritive proteids become united to cells in the course of normal assimilation, the term 'haptophore group' being applied to the group of atoms by which either the toxin molecule or the nutritive proteid molecule becomes attached to the receiving group or 'receptors' of the cells. The resemblance between the physiological assimilation of proteid and the union of cell receptors with toxins is illustrated by the fact that both nutritive proteids and toxins are capable of inducing the formation of 'anti-bodies' which stand in a specific relation to the stimulating agent. . . . The introduction of a toxin is followed by an excessive production of receptors which are finally thrown off into the circulation as unused ballast. The free circulating receptors are the antitoxin" (Herter, "Lectures on Chemical Pathology," page 11). The "side chain" theory of immunity enunciated by Ehrlich seeks to explain the formation of antitoxin by a chemical affinity established between poisons and certain constituents of cells. Chemical compounds possess not only a central group of atoms, but lateral groups as well, and it is these that are more liable to be attacked by the toxin, the central group perhaps not suffering at all. A close union is established between the toxins and side chains of protoplasmic molecules which may or may not interfere with the vitality of the cells. On the other hand, the cells are stimulated to produce fresh "side chains" which, becoming detached, circulate in the blood as antitoxins.

As might be expected, there have been many objections raised to this interesting "side chain" theory of Ehrlich. Metchnikoff fails to see in the chemical theory any satisfactory explanation of immunity. In the leucocytes and their phagocytic action is to be found, according to him, those biological processes that create immunity. There is much to support the contention, that it is from healthy living cells and not from those that are diseased or injured that antitoxins are formed, since there are normally present in the blood of certain animals specific antitoxic bodies.

It is the function of the gastro-intestinal juices, aided by the movements of the stomach and intestine, to convert foods into such soluble forms that they can be utilized in the economy. Landois and Stirling show how undigested proteids and their derivatives may be acted upon by fungi. "Many fission fungi—

*e.g.*, bacillus subtilis and the spirillum of cheese—can produce a peptonizing ferment; so that a small amount of the peptonizing done in the intestine may be due to microbes." This, though not proved, has been rendered probable by the experiments of Vignal. "From the normal intestinal mucus Babès has isolated five species of bacteria, while an enormous number of micro-organisms exist in the large intestine and fæces. All these organisms resist the action of the digestive fluids, save a few, which are dissolved by the gastric juice. The researches of Duclaux, Vignal, and others have shown that certain of these micro-organisms secrete soluble ferments identical in their action with the ferments of the digestive juices. Vignal states that certain of these organisms contribute to the dissolution of food in the intestine. It is certain that they contribute to many processes of fermentation and decomposition which go on in the intestine. During fœtal life these organisms are wanting, but they are numerous a few days after birth. In this connection we cannot fail to remember that bacteria by their action can produce in albuminous fluids albumoses and peptones, and that the former bodies are now regarded by bacteriologists as substances which play an important rôle in many pathological processes" (Landois and Stirling, "Physiology," page 344).

Metchnikoff has demonstrated that man is born free from microbes. Their first implantation occurs in the act of parturition, for soon after birth the skin and mucous membrane become infected with them either from the air or from the water with which the infant is washed. As early as four hours after birth bacteria have been found during warm weather in the intestinal contents. Usually this is delayed until ten to seventeen hours afterward. It is in the intestinal tract that microbic flora grow most abundantly and it is observed that these vary with changes of diet whether purely vegetable or animal. Their presence is independent of food, for micrococci and bacilli have been found in the meconium of infants before any nourishment has been taken. No sooner almost is a baby given his mother's milk than variations occur in the microbes of his intestine: the bacillus bifidus appears. Cows' milk also favors the development of this micro-organism along with the colon bacillis, streptococci, staphylococci, lactic acid bacilli, etc. According to Vignal and Suckdorf, an adult man passes daily in his fæces from 30,000,000,000 to 50,000,000,000 of bacteria. The harm these micro-organisms do is through the products which they form and which, when absorbed are toxic—*e.g.*, indol and skatol. Although many of the bowel micro-organisms in health are apparently harmless, they can yet become extremely virulent when their surroundings are altered, as is seen in accidental kinking of the intestine, internal strangulated hernia, or in a limited muco-enteritis.

Bouchard, in "Auto-intoxication," clearly indicates that man is constantly standing, as it were, on the brink of a precipice; he is continually on the threshold of disease. Every moment of his life he runs the risk of being overpowered by poisons generated within his system. Self-poisoning is only prevented by the activity of such excretory organs as the kidneys, and by the watchfulness of the liver, which acts the part of a sentinel to the materials brought to it by the portal vein from the alimentary canal. Disease is not something altogether apart from the individual. The patient and his disease are too often found living under identical conditions.

Sir Lauder Brunton, in his "Introduction to Modern Therapeutics," devotes considerable space to the discussion of this all-important subject. Chemical investigation has shown how disease depends upon the products of putrefaction and fermentation, rather than upon the direct action of microbes upon the tissues. It is this fact which renders knowledge of the life-history of bacteria so valuable to us, for, long after microbes have been destroyed, the enzymes, or ferments, which they formed continue to act, and are not destroyed by a temperature which is destructive to the organisms themselves.

Scarcely a month passes without a death being reported and traceable to a meal of tainted meat. Sir Thomas Stevenson, of Guy's Hospital, has recently demonstrated the far-reaching and fatal consequences of such a diet. I myself have reported in the *Lancet* a case of acute peripheral neuritis, ending in rapid death, and due, in all probability, to certain viands consumed at a particular banquet. The cooking of meat tainted by microbes, while it is destructive to the organisms, may yet allow the ferments they have formed to carry on their work of decomposition. It is thus that the cold meat or beef-steak pie which forms the principal part of a Monday dinner, though eaten with impunity when hot on the previous day, becomes a source of danger. Of this I had a striking illustration a few years ago, in the Industrial Schools of this city, to which I happen to be honorary physician. A certain Sunday dinner of roast beef had been enjoyed by all the inmates of the school. On the following Tuesday morning there was an epidemic of diarrhœa in the school such as had never been witnessed before, there being upward of one hundred cases. Several of the older lads were not slow to express the opinion that their food had been drugged by materials taken from the surgery. The case, however, was perfectly clear. Those children who had not partaken of the slightly-warmed-up cold meat left over from the Sunday dinner—although placed under the same dietetic conditions, except as regards that one particular meal—alone escaped. It is to subjects such as these that Bouchard draws special attention, and of which I might still further write.

An almost similar event happened in a Northumberland village just before going to press. I was summoned to see a family, four of whom were extremely ill through having eaten fish recooked in the form of pie. Fresh cod, apparently healthy, had formed part of the *menu* for the early dinner. The remainder was served up as pie the same evening. The husband and wife and two grown-up daughters who had eaten the pie at supper were seized during the night with vomiting and purging, followed by extreme collapse, cold perspiration, irregularity of the heart's action, and feeble pulse. Only in the case of the husband did the temperature rise slightly above the normal. He also had severe headache. The symptoms of collapse were pronounced in all the patients. As only those inmates of the house suffered who had eaten the fish pie, clearly some chemical change had occurred in the cod between midday and evening. These cases resemble those described by Professor Bouchard on page 157.

Setting aside the chapters on the "Toxicity of Urines," in which Professor Bouchard is, perhaps, seen to greatest advantage, the lectures devoted to typhoid fever and cholera contain suggestions of considerable value from a therapeutic point of view. It is only lately we have come to recognize that, once the dangers incidental to typhoid fever have been successfully surmounted, there are risks yet to be overcome—in a word, auto-intoxication from poisons generated within the intestinal canal. There are few medical men who have not had some experience of the success which has followed the administration of intestinal antiseptics in enteric fever. In my own practice I have used betanaphthol with excellent results. I can recall one case in particular, where a young gentleman, in the fifth week of enteric fever, was so prostrated and blanched by intestinal discharges that he could not be turned in bed without fainting; he had an almost imperceptible pulse, a temperature of 105° to 106° F., was almost *in extremis,* and whose life I consider was saved by betanaphthol and other intestinal antiseptics. We know that naphthalin is sparingly soluble, and that it passes to a large extent unchanged through the alimentary canal. No one denies to it the power of destroying the disagreeable odor of the motions. Salol, or the salicylate of phenol, has also given excellent results. Having passed through the stomach undecomposed, it comes into contact with the pancreatic juice in the duodenum, and is thereby split up into salicylic and carbolic acids. The latter is set free where it is required, but, as Brunton says, it has the disadvantage of being poisonous, and so betol or salicylate of betanaphthol is to be recommended instead. All the substances belonging to the phenol class may be regarded as antiseptics in the largest sense of the word. Outside the system they readily arrest the development of germs, but within it their action is not so definite. They are antiseptics so long as they are not absorbed. Once this occurs, the antiseptic power of the phenols is suspended. They then form non-antiseptic compounds, Hoelscher in his experiments having shown that the blood does not become sterile even after large doses of guaiacol.

A fairly large experience of the treatment of certain diseases in which the blood is poisoned—*e.g.,* ulcerative endocarditis, etc. —has led me to place considerable reliance upon phenols. When absorbed they no longer exercise a direct action upon the germs, but they exert another influence, viz.: a depoisoning one. Seifert and Hoelscher maintain that when the phenols are absorbed they induce a depoisoning of the body by combining with and eliminating the toxic albumins produced by the action of morbific germs. Phenols are not found free in the blood. They are eliminated in the urine as ethereal sulphates, in the form of salts that have resulted from the oxidation of some compound of the phenols with albumin, and, to a large extent, with toxic albumins, the result of the vital activity of germs. It is believed that the compounds of toxic albumins and phenols are non-toxic. They quickly undergo oxidation; hence the appearance of phenols in the urine as ethereal sulphates. Chemical disintegrations and recombinations undoubtedly occur, and to these must be attributed, by the process of depoisoning just described, the good results that follow the administration of antiseptics in certain forms of blood-poisoning. Under circumstances similar to the above rigid intestinal antisepsis cannot but be of the greatest utility.

Salols pass through the stomach without undergoing decomposition. In the small intestine salols and phenols are split up into their antiseptic constituents: salol into salicylic and carbolic acids, betol into salicylic acid and betanaphthol, while guaiacol carbonate—the new remedy for phthisis—decomposes into guaiacol and carbonic acid.

I shall leave the reader to follow Dr. Bouchard in his criticism of cholera and its relation to the comma bacillus.

The part played by auto-intoxication in mental diseases is attracting attention. In the *Medical Week,* August 11, 1893, there is a lengthy report upon the subject as discussed, at the French Congress of Psychological Medicine, by Drs. Régis, Chevalier-Lavaure, and others. It has long been known that the various fluids of the body undergo modifications in the insane. Recent investigation has shown that the urine is much less toxic than normal urine in cases of mania, while the lethal action of this fluid is increased in melancholia. The urine of maniacal patients gives rise to excitement and convulsions when injected into an animal, while the injection of urine from a case of melancholia is followed by depression of spirits, restlessness, and stupor—a proof that auto-intoxication is the cause, and not the effect, of the mental condition. Besides, in the mental disorders that arise during the course of such infectious diseases as typhoid and other eruptive fevers, as well as in puerperal fever, there is little doubt that many of these disturbances are due to the action of pathogenic organisms directly, or indirectly through the influence of their toxins; according to the stage of the illness, so is the character of the mental symptoms. By no physicians more than those resident in lunatic asylums has the subject of autotoxis been so carefully studied. The administration of a large dose of calomel, followed hours afterward by a saline purge will often clear a patient's mind as well as relieve his body during the delirium of acute mania. Toward the terminal stages of chronic interstitial nephritis and diabetes, etc., psychoses of an hallucinatory nature are not unknown. They are due to impaired cerebral nutrition or to the circulation of some form of nerve poison in the blood consequent upon defective elimination. To imperfect emunction is attributed the disagreeable odor so frequently observed in the insane. One has only to mention these facts to throw into bold relief the excellent results that frequently follow the administration of antiseptics and excitants to the emunctories.

This translation is given in the hope that English readers may find in its pages much that is interesting from a pathological point of view, and much that is valuable and suggestive from a therapeutical. For mistakes attributable to myself I crave indulgence. As a translation, I am only too conscious that the work is far from being perfect. If, however, the book serves a useful end, I shall be fully repaid for the time and labor I have spent upon it.

I cannot draw this preface to a close without thanking Professor Bouchard for the freedom he has allowed me in translating and publishing this work.

In this (second) edition the new matter interposed in the text by the editor, and for which he alone is responsible, is inclosed in brackets [].

THOMAS OLIVER.

7 ELLISON PLACE, NEWCASTLE-UPON-TYNE.

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# LECTURES ON AUTO-INTOXICATION.

## LECTURE I.

### PATHOGENIC PROCESSES IN THE MAIN.

**Preponderance of pathogenesis in the preoccupations of contemporary medicine. The four great pathogenic processes: primary elementary dystrophies; nerve reactions; previous disturbances of nutrition; infection. Influence of earlier disturbances of nutrition upon the production of most of the chronic and of many acute diseases. Definition of diathesis considered as a morbid temperament.——Infection. Living nature of contagious matter. Small number of diseases for which parasiticism has been established with certainty. Extreme probability of the hypothesis according to which all contagion might be the function of a vegetable organism. The part which medicine plays in the presence of the doctrine of micro-organisms. The abundance of microbes around man and the relative infrequency of infection. Association and combination of pathogenic processes. The powerlessness, as a rule, of nervous reactions to determine by them alone disease.——Morbid predispositions established by the arthritic and scrofulous diatheses. Disease opportunity. Diathesis of short duration established by a nervous reaction, which interferes for the time being with nutrition, and opens the portal to infection. Diathesis acquired. Diathesis hereditary. Interrupted accidents in the course of diatheses.——Bond between new discoveries and traditional medical observation. The physician has a double duty: to contend with microbes and to fortify the organism against them.——How disturbance of nutrition may produce disease. Intoxication of the organism by increase or retention of normal matter. Intoxication by the formation of abnormal matter.——The part intoxication plays in the processes of infection. Five hypotheses relative to the mode of action of pathogenic microbes. Toxæmia of pregnancy. The rôle of microbes in the formation of certain poisons normal to the organism.**

#### GENERAL PATHOLOGY.

WE are living in an age when it is proper to live and when all are interested in medical matters. It is not that medicine has, in any sense of the word, revived, but that she has simply changed her attitude of observation.

After having devoted herself during many long years to the verification of symptoms, to the research of anatomical lesions, to the study of pathological physiology, she comes at last to study the origin of disease. What is characteristic of these modern days, so far as medicine is concerned, is the high place we assign to the study of the origin of diseases.

If the causes are innumerable, you know that the processes following those which induce disease can be relegated to four types. These four chief pathogenic processes are: (1) primary elementary dystrophies, (2) nerve reactions, (3) disturbances antecedent to nutrition, and (4) infection.

The first of these processes is the most simple, but it is the least studied, and I may add that it is almost completely unknown. It is that which arises from the vital activity of cells, and is directly brought under our notice by some cause, physical, mechanical, or chemical; from the lightning-stroke to the intoxications, or by traumatism. If one neglects more than is necessary the study of that simple process, it is because very often it is complicated with effects of a local character, vascular or otherwise, which are the reflex result of nervous requirements.

We have known for a very long time the important part played by the nervous system as an intermediary in the production of disease. Have we exaggerated it, or have we accorded to the reflexes a pathogenic influence greater than that which they have in reality? When they are set in operation in a person in good health they only rarely cause the development of the malady properly called; their rôle is often to bring about fleeting indispositions or troubles, for a longer or shorter period, to the extent of realizing predisposition or the morbid opportunity.

You know that those pathogenic influences are peripheral or central. It is in their action upon the cutaneous nerve endings that cold and moisture interpose as a cause of disease; it is by their direct action upon nerve centers that disorders of the affections, changes of disposition, mental fatigue, and so many other psychical disturbances frequently bring about deteriorated health. Generally speaking, it is only a condition accessory or predisposing to the development of the disease; it is rarely the nearest or exclusive provocative cause.

The two other pathogenic processes of chief importance are disturbances antecedent to nutrition and infection. Disturbances of nutrition rule, in my opinion, the largest number of chronic diseases, and explain the appearance of many illnesses of an acute character. I had devoted to this study the first years of my profession, and I have returned to it when I have tried to determine the exact domain of diathesis and the processes by which we can undertake the cure of diathetic diseases. My constant effort has been, and my duty will, perhaps, be, to render to diatheses the part which is theirs by right in the prejudices of medicine. To do that, I have been obliged to disengage them from the mystic cloud which encircled them, and I have rendered them physiologically intelligible when I have said that diathesis is a permanent disturbance of nutrition, which prepares, provokes, and maintains different diseases, as seen in their location, their evolution, and pathological process. This was to restore to diathesis its traditional signification; it was to consider it anew as a morbid temperament.

Infection is the last of the four pathogenic processes. We find, again, traces of this notion very far back in the past, but it has assumed form only within the last quarter of this [now passed] century. It is what we call, or it is what, now particularly, deserves to be called, *contagium vivum.*

The interpretation of infection has provoked the warmest discussions in our times. The brilliancy of certain recent discoveries has been to fascinate and to dazzle. It has caused, according to temperament, enthusiasm or sarcasm, infatuation or dread. Infatuation or dread,—these are two sentiments which science repudiates. She will continue, in spite of resistance, and in spite of the intemperate displays of an exaggerated enthusiasm, to march, serenely and unmoved, toward truth.

At the present time the living nature of contagious material is beyond all question. Ever since man has known contagion he has been asking himself of what it might consist. Of all hypotheses, not one has been verified, until the day in which it has been demonstrated that in the body of an individual attacked by a contagious disease there exist the lower vegetable organisms, capable of implanting themselves and of multiplying in the tissues of a healthy man, and of determining in him a disease similar to the original. That is the final termination of all systems relative to contagion.

Demonstration has not been made for all contagious diseases; doubtless it is not even complete, save in a number more limited than we maintain. Parasiticism is established with absolute certainty in four diseases of man,—charbon, glanders, tuberculosis, and gaseous gangrene; besides, proof is nearly established in blennorrhagia and erysipelas. To these diseases of men we may add several experimental septicæmias,—the cholera of fowls, swine fever, and symptomatic pustule. This is a small number, and yet it is large if we consider that in those cases alone where infection could be interpreted in a positive manner the solution has been universally agreed upon. Contagion has always been recognized as the function of a vegetable organism.

Have we the right to generalize, and can we say that it is always due to the transfer of a vegetable from the contaminating to the contaminated individual; that in all these cases infection is the result of the introduction into the economy and of the multiplication of a vegetable parasite? No, absolutely; yes, if we are content to enunciate an extremely probable hypothesis. We surely except nervous contagion, which results from example.

In regard to diseases of a contaminating nature, every time that we have found an explanation of contagion it has been that which I have just given you; no other has been verified, no other is verifiable.

Let us admit, then, at least provisionally, that each contagious disease is produced by a microbe. Let us wait until positive proof shall be furnished for those in which the microbe has not yet been demonstrated. We will accept without astonishment the announcement of its discovery, and without uneasiness the delays which might be caused by that demonstration. Let men trained to the difficulties and to the refinements of microbiological research give us this fulfillment of demonstration, and it will be with thanks that we will praise every one of their discoveries. The rôle of the physician is not exclusively to seek the infectious agent; but it ought to count with him. To speak of microbe in the place of virus or of contagion is not to replace one word by another; it is to substitute positive knowledge for ignorance or whim. It is, at the same time, to state this eminently practical question: What are the conditions which render possible the development of the microbe? What are the conditions which may hinder its multiplication?

What renders possible the development of an infective disease is not the chance meeting of man and microbe. This meeting is constant, but it is generally without result. Microbes, even the most dangerous, assail us. They are spread around us with the same prodigality that nature distributes developing matter, and yet infection is uncommon. Infectious disease, too, is only an accident, because the morbid agent finds only exceptional circumstances favorable,—I do not say to its penetration, but to its development and its multiplication.

The healthy man is not attractive to the microbe. While almost constantly invaded by infectious agents, he reacts against them, and in this contest he keeps generally uppermost so that often the disease does not even become apparent.

It is not thus with the man whose vitality is weakened; then his means of defense diminish. Just as we see rushes become covered with soil where certain unusual circumstances are opposed to the natural flow of water, so certain microbes may invade the human organism, whose health breaks down, whenever, by the fact of disordered nutrition, the chemical constitution is modified.

It is, therefore, a modification antecedent to nutrition which renders infection possible. Disease is thus the result of two different processes, one of which can only act by means of the other. In short, pathogenic processes are rarely isolated; in the great majority of cases they are associated and combined.

In regard to this complexity, you do not find it only where there is question of contagion, but also where there is question of the most simple form of disease,—traumatism, for example. In those primary and elementary forms of failure of nutrition where the cause directly attacks certain cellular groups, where the cells become detached from each other,—crushed, soddened,—disease will scarcely ever be established by this unique disorder of a cellular group. Nearly always traumatism will determine the putting into operation of new pathogenic processes, infection, and nerve reactions. Disorganization of cells allows the entrance of infectious agents, and prepares in them the matter that they should destroy. Besides, the cause which is capable of inducing alterations falls oftenest upon the nerve elements, and through them, as an intermediary, provokes reflex disturbances. Some manifest themselves in the wounded part, where the irritation of blood, absorption, and nutrition cause work to be done in an abnormal manner. Others reflect upon the whole economy; the heart contracts oftener, respiration is accelerated, and the elaboration of material is found altered in all the cells of the body. Urea and carbonic acid are produced in much greater quantity. Nerve reaction has not only added certain peculiar features to local manifestations, it has bound the whole organism to the work which is going on in the wounded part.

Besides, nerve reactions nearly always borrow the co-operation of another pathogenic process. Every nerve excitation, cold, shock, emotional or traumatic, may produce syncope, epistaxis, diarrhœa, and polyuria. These are not, then, diseases. The real disease, when it is roused by nerve reaction, infers,—except in cases where the intensity of the stimulation is excessive and those wherein the nervous system is abnormally excitable,—infers—do I say it?—an essential deterioration of the organism.

In whom does a draught of cold determine a coryza or a bronchitis? In everyone, will you say? Perhaps; but especially in those whose health is habitually or actually altered. Among the diathetic, especially arthritic or scrofulous, you will see this fleeting nerve reaction produce in them lasting effects; the coryza is tenacious and the bronchitis is stubborn. Disease will quickly follow upon nerve reaction, but it is the unavoidable deterioration of the organism which may hasten its explosion, and which often renders it persistent and chronic. In the nondiathetic man, for the present weakened or indisposed, disease resulting from nerve stimulation will be not less prepared by disturbance of nutrition, although the disturbance is only transitory,—"it is the morbid opportunity," the brief diathesis of the authors of last century. Men fatigued by overwork or pleasure—exposed to depressing influences—are struck by conditions, real and disease-developing, from insignificant nerve excitations which would have produced nothing in perfectly healthy men.

Very often disease induced by nerve reflex—even disease from cold—is an infectious illness, and we have not only in this particular case a new example of the association of the two different pathogenic processes, but we find here the association of a third factor. In reality, nerve reaction could not have created infection: it could act only by rendering this infection possible; by weakening the defense which the healthy organism naturally opposes to microbes: by modifying nutrition so as to develop a chemical medium favorable to the cultivation of vegetable organisms. The reaction of a disturbed nervous system induces temporary disturbance of nutrition. This, in its turn, opens the way to infection always at hand, to germs always present, which, without doubt, have to fulfill in nature another part, but which, destined to destroy dead matter, are also capable of destroying living matter when they find it in a state of preparation. In this, perhaps, lies the pathogenic history of angina, of pneumonia, and of rheumatism.

If nerve reaction, by corrupting for the moment nutrition, can produce the morbid opportunity, it may also modify nutrition in a lasting manner, and develop diathesis, but it will be the acquired diathesis. The acquired diathesis, once established, may become hereditarily transmissible; and if you go back to its etiology, be it in the individual or in his ancestors, you will easily recognize that it has had for its origin the putting into abnormal play of nerve reactions. Let a bad alimentary hygiene—cold and moisture, privation of air and light—cause an infant to be scrofulous, and let the permanence of the same causes keep up in him this nutritive disorder, which we designate under the name of scrofulous diathesis; or let a young man, by hygienic errors, by the abuse of the table, by protracted studies at night, by venereal excesses, by nervous shocks, which may be the consequence of complete derangement of mind, as also of a jaded brain, develop this other nutritive disorder, which we designate under the name of arthritism,—in both of these each cell will have a tainted nutrition, and will produce cells that maintain the same nutritive type. And among these cells the generative elements—ovule or spermatozoön—in their turn will give birth to the cells of a new being, whose nutritive activity will be similar to the individual that has begotten them. The acquired diathesis has become hereditary; it does not recognize for its cause in the descendants the vice of their own nerve reactions. In these, nevertheless, the diathetic state really arises from nerve perturbations experienced by their ancestors. There are certain historical families whose pathological genealogy we ever know, and where the reality of the origin of these morbid states can be verified.

The diathetic nutritive disorder is more than a morbid threatening; it is disease in activity. But how is this disease going to break out? It is generally after the operation of an external cause which has induced nerve changes: another example of the necessary association of several pathogenic processes. Here is an arthritic; how will he be seized with an attack of gout? Very often after a chill, a shock,—emotional or from injury. Disease thus called forth in the course of a diathesis is an episode, a paroxysmal accident; but this accident, this episode, may appear spontaneously, as the consequence of the excess of the nutritive disorder which oftenest recognizes as its determining cause nerve change. Some people persist in not making this distinction, in not seeing in gout anything but the gouty accession; so much so that gout would not be a disease, but a succession of independent diseases. But what explains and links the attacks together is precisely this diathetic state, which I consider the result of a failure of nutrition. The attack of gout, on the contrary, which is the paroxysmal accident in the course of a diathesis, is characterized by an acceleration of nutrition, as I said a long time ago, and is repeated to-day, as if it were a novelty: it is the curative attempt which re-establishes the broken equilibrium.

If nerve shock is capable of thus inducing an attack of gout in an arthritic it will never cause it in an individual whose nutrition is not weakened. The nutritive derangement which renders possible the pathogenic influence of nerve reactions favors also parasiticism. Is it not among arthritics that you see developed by preference pityriasis versicolor? Is it not among the scrofulous that you see erysipelas repeated with a truly disheartening frequency? I have multiplied examples sufficiently to be able to say that, without any preliminary change in nutrition, man is sheltered from infection. I have excepted syphilis, against which he seems unprotected. It is because several pathogenic conditions are necessary before disease can be produced that we generally resist harmful influences. The causes of disease are innumerable; but, in order to attack and conquer us, they must be associated; without this necessity they would, without doubt, have annihilated the human species.

Thus, only to deal with infectious diseases, I am right, you see, in telling you that the physician ought not to allow himself to be absorbed alone in the research after a microbe. He ought to occupy himself with the infectious agent; but he ought also to retain a good deal of his anxiety for the study and research of circumstances which disarm the organism against the invasion of that agent. When the physician shall be in possession of this double knowledge that many diseases are produced by microbes, and that these can only act by means of a deterioration of the health, resulting from various pathogenic processes, he will recognize that the new discoveries contain nothing subversive, and that the lessons taught by ancient medical observations are not compromised; he will know that the part he has to play is still the same to-day as it was twenty years ago, and that whilst seeking the means of combating microbes he ought and he will always be obliged to sustain the forces of the organism and make good its defense, inspiring himself constantly with this truth: before every illness there is a disturbance in life,—for nutrition is life. What can bring about this disturbance,—the first step to be overcome before becoming ill? It may bring about a change in the production or distribution of the forces which liberate certain substances elaborated by the living organism. It may modify the matter itself,—augment or diminish it,—while preserving the normal proportion, or it may bring about disproportion of the constituent elements; it may, in short, cause the appearance of abnormal substances through perversion of the changes associated with nutrition. From absolute increase of normal matter, or the production of abnormal, intoxication may be developed.

Substances the most essential to the constitution of the body may become hurtful when they accumulate. If the subtraction of water is dangerous, its excess is none the less so; it changes the conditions of osmosis; it causes a swelling up of the cells, and washes out their dialyzable material; it thus disturbs their chemical constitution, and weakens or perverts their functional activity. Mineral substances can, by their excess, equally determine accidents that are truly toxic,—the salts of potassium particularly. The most important excrementitious material—carbonic acid—could not be retained in excess in the organism a few minutes without death being the consequence. The biliary acids also, if they do not find a free escape outwardly, produce fatal poisoning. All the soluble ferments elaborated by certain glands can exercise a poisonous influence, either local or general. We find even in certain secretions—in saliva, for example—products extremely toxic, and which are not ferments. This toxicity is only partly due to alkaloids. Whatever opinion we may have in regard to the origin of alkaloids, it is certain that we meet with them in normal tissues, and it is possible that they may be one of the results of this disassimilation of animal cells; but it is not demonstrated that these alkaloids of the normal tissues are toxic. It is not thus, however, with the alkaloids of certain products of secretion,—of urine in particular. Without multiplying examples, you see that the augmentation of normal substances, either by increased formation or retention, can induce quite a series of toxic accidents, some of which have already been named, such as asphyxia, uræmia, uricæmia, cholæmia, glycæmia.

Perverted nutrition leads up to the development of new substances which may become toxic. There are often formed in the organism peptones, which are injurious in this sense, that, being dialyzable, they escape by the urine, and thus bring about an abnormal spoliation of the organism. There are thus produced abnormal albumins, which escape by the kidneys, and seem capable of destroying the nutrition of the renal epithelium and of inducing certain forms of nephritis. Disease also causes the appearance of abnormal coloring matter or of substances transformable into coloring matter, among which are found those that, in urines, take on a red coloration under the influence of perchloride of iron—*e.g.*, acetone. I also mention leucin, tyrosin, and the imperfect excrementitious products which arise from insufficient elaboration on the part of the liver; many other toxic substances, too, of which I know neither the names nor the constitution, but whose presence in morbid urines I shall demonstrate to you physiologically. All these substances are capable of producing forms of intoxication, among which I will mention eclampsia, acholia, diabetic coma, and many other grave conditions, as also numerous indispositions.

[During pregnancy poisons are formed in the mother and fœtus which circulate in the maternal and fœtal blood. Upon the mother is thrown the burden of eliminating by the kidneys, liver, intestine, skin, and lungs the bulk of the poison formed within the two organisms. When these poisons are retained auto-intoxication is produced which varies in degree from heightening of the arterial tension, headache, gastric disturbance, and lassitude to convulsive seizures as in puerperal eclampsia. The urine under these circumstances usually contains albumin. That errors of diet often induce puerperal eclampsia there is no doubt. I have seen pregnancy advance normally until some such improper food as lobster, pork pie, etc., was eaten ravenously, when as the result of the entrance into the blood of imperfectly digested products or intestinal poisons eclampsia followed. The presence of these toxins in the blood induces structural alterations in the renal epithelia and as a consequence renal *débris*, tube casts, are present in the urine along with albumin. If the patient lives, the morbid changes are, for the most part, temporary, for they disappear on cessation of the pregnancy. We are familiar with the dropsical legs of women seen near the end of pregnancy, but it occasionally happens that there is in addition to the auto-intoxication from intestines and kidneys, an hepatic toxæmia as well. The liver becomes enlarged and tender, the patient slightly icteric, the stools pale, fluid appears in the abdominal cavity, and there are albumin and bile in the urine. It is not until the pregnancy has been brought to a natural or an artificial termination that the symptoms and physical signs disappear. In such a case the liver has failed to arrest and destroy the intestinal poisons as they pass through it and the result is that owing to their excess in the blood and inability on the part of the kidneys to eliminate them the patient is poisoned by products formed within her own body.]

If intoxication is one of the accidents likely to arise from disturbances of nutrition let us see what infection can do. We have thought over many of the hypotheses bearing upon the mode of action of microbes. But if the anatomy of these hurtful agents is scarcely known their physiology is still less known. We have imagined that they act in five different ways. We have ascribed to them a mechanical rôle, supposing that they might cause obstruction in the vessels, more particularly those of the lung and the kidney. The fact is perfectly demonstrated for charbon and for the septicæmia of Charrin; but the microbes which live in the blood are rare—almost the exception. It is also admitted that they may induce traumatic changes,—erode and perforate cells. This is an hypothesis whose aid I called in when I established the group of infectious nephritides. We find microbes in the organism,—in urine,—and there is perhaps a lesion of the renal epithelium. It is admissible that they have broken through this epithelial barrier, and that in their course through it they have brought about its deterioration; but in this there is only probability. The history of the cholera of fowls proves to us that microbes attack muscular fiber; in certain catarrhs of the bladder and vagina they penetrate in large numbers the epithelial cells. I have demonstrated in blennorrhagia that the micrococcus of Neisser inhabits essentially the protoplasm of the pavement cells of the urethra or of the conjunctiva, and that the leucocytes are for it an accessory or secondary resting place.

It is also said that microbes cause death by the anatomical lesions which they develop. Assuredly there is among them some which produce œdema, hæmorrhage, suppuration, emphysema, and gangrene; but to say that they act because they produce these effects is to solve the problem by admitting as demonstrated that which is still a matter of discussion; the essential thing would be to know by what process they determine such local lesions.

A fourth hypothesis has been enunciated, viz.: that the microbe, in order to nourish itself, consumes what is useful, and it is the subtraction of this which is prejudicial to the organism. The example of charbon has been quoted in support of this contention; its aërobic bacteridium takes hold of the oxygen to the detriment of the blood-corpuscles. This ingenious hypothesis has not even received the beginning of demonstration.

Last, infectious agents can produce something injurious,—can elaborate substances that are toxic. There, at least, and there only, do we find a beginning of the proof. Indeed, we know a good many bodies produced by the life of microbes. We have studied, in the fermentations which they induce in the flask, carbonic acid, marsh-gas, hydrogen, even sulphuric acid, ammonia, the ammonia compounds, the volatile fatty acids, many complex alkaloids whose toxicity has been experimentally demonstrated, indol, phenol, skatol, etc.; all can poison, for these bodies are toxic. They form besides, soluble ferments, which undoubtedly play a part in the production of local lesions by breaking up in some way or other living cells. It is therefore certain that intoxication in part arises from the harmful action of microbes; in all probability such is the part they chiefly play.

It is not only in infectious diseases that we have to reckon with the intoxication produced by them, it is also in the normal state. Indeed, man, in the condition of physiological life, is inhabited, for a considerable length of his digestive tube, by microscopical vegetable organisms. I have formerly shown you the toxicity of intestinal matter; it is in part due to the poisonous products elaborated by these microbes. A portion of these products is absorbed, disease may prevent their elimination, and there arises from this a poisoning. Intestinal fermentation increasing abnormally, the accumulation of toxic matter may become such that absorption produces intoxication in spite of the integrity of the renal emunctory; it is to this cause that many dyspeptic accidents should be referred. Thus, in the normal as well as in the pathological state the organism is a receptacle and a laboratory of poisons.

The object of the lectures which follow will be to find out what part is played by self-intoxication in the production of disease and morbid accidents.

# LECTURE II.

## Production and Elimination of Poisons by the Organism.

The healthy organism receives and forms poisons. Constant danger of auto-intoxication. Means by which the organism manages to escape from it.——Origins of poisons in the healthy organism; alimentation, especially mineral substances; the secretions (saliva, bile); digestion and intestinal putrefactions; disassimilation of the tissues. The blood is the ebbing and flowing current of all the poisons.——Demonstration of the presence of poisons in the blood. Direct demonstration is still incomplete. Indirect demonstration: we find in the urine, naturally or modified, the same poisons as in the digestive canal and in the tissues; they must, therefore, have traversed the blood.——Opinions offered to explain the harmlessness of the poisons of the digestive canal. Destruction or modification by dialysis in passing through the intestinal mucous membrane, the epithelium, and the capillaries (Stich). Hypothesis relating to the white cells. Protective part played by the liver, which stops on their passage alkaloidal poisons coming from the intestine (Heeger), and destroys them. Experiments of Schiff.——Rôle of the emunctory organs in the expulsion of poisons. Intestinal emunction: the putrid diarrhœa of anatomists; salutary diarrhœas. Illusions relative to diarrhœa spoken of as supplementary to the renal emunction. Cutaneous emunction: elimination of water; perspiration favorable to elimination of poisons. Elimination of volatile fatty acids: odors arising from the skin when nutrition is deranged. Causes of the death of animals which have been varnished.——Pulmonary emunction, carbonic acid, water, volatile fatty acids; fetidity of the breath in those who are constipated and in hypochondriacs.——Renal emunction: its preponderating influence. The kidney can eliminate all toxic products except gas. Toxicity of urine: danger of oliguria: critical polyuria at the decline of fevers. Toxicity of sweat.

I have said that the organism, in its normal, as in its pathological state, is a receptacle and a laboratory of poisons. Among these some are formed by the organism itself, others by microbes,—minute forms of vegetables,—which either are the guests—the normal inhabitants—of the intestinal tube, or are parasites at second hand, and disease-producing. Man is in this way constantly living under the chance of being poisoned; he is always working toward his own destruction; he makes continual attempts at suicide by intoxication. And yet this intoxication is not realized, for the organism possesses numerous resources which enable him to escape the intoxication which is always threatening. He throws off these toxic substances into a special reservoir, from which they afterward pass outward; and, besides, the blood contantly subtracts from the organs the poisons as soon as they are formed in them.

I have shown in the first lecture how numerous are the toxic substances contained in the organism. In the first rank are placed the mineral substances introduced with our food; then, come the products of physiological secretion,—saliva and bile; the products of digestion; digestion, too, while it transforms albuminoid substances into peptones, also give birth to alkaloidal poisons; and, last, toxic substances resulting from intestinal putrefactions. Without doubt, the stools eliminate the greatest part of these poisons which are expelled with them, but, nevertheless, owing to the slow movement of the intestinal contents, the mucous membrane absorbs a certain part of them. We find in the close relationship of our tissues other poisons which are the result of the life of cells. They pass out into the extracellular fluids, along with which they pass into the lymphatics and blood-vessels. It is, therefore, into the blood that all the poisons are carried,—the whole of those that are made by the tissues, and part of those which are formed in the digestive tube. Theoretically we cannot conceive how things could be otherwise. But, evident even as this view of the subject appears, it must be demonstrated. Direct demonstration of it has only been realized in a very incomplete manner. After ligature of the colon, Planer found $H_2S$ in the blood of the portal vein. Carter has there met with indigo in animals the subjects of intestinal derangements. I have seen, like Gautier, alkaloids not only in the tissues, but in the blood. Here is a beginning of direct objective demonstration, but it is only yet a resemblance. It is not a certainty.

On the 4th of December, 1884, we extracted, by means of chloroform, alkaloids from 50 cubic centimeters of muscle of beef. These alkaloids, soluble in chloroform, give precise reactions with the following reagents: Tanret's solution, iodized iodine, phosphomolybdate of soda and tannin. September 3, 1884, a healthy rabbit is killed, then cut up into pieces; it weighs thus minced, without the abdominal viscera, 1012 grams. It is digested in 2 liters of absolute alcohol, to which has been added water acidulated with $H_2SO_4$, and this mascerates for two days. We collect the alcohol as it is filtered, and again unite it to the alcohol which bathed the muscles of the animal, and which we obtain by pressure. We have thus 1896 cubic centimeters. We evaporate at 40°; then the alcohol, reduced by one-third, is evaporated at 80° (we lose by accident one-third of this). In the watery residue we find all the reactions usual to alkaloids. The precipitates obtained are abundant with the following reagents: Tanret, iodized iodine, phosphomolybdate of soda, ferric cyanide, double iodide of potassium and cadium. This residue, made alkaline by soda, is mixed well with ether. We decant the ether, which, shaken up well with a little HCl that has been added to it, is distilled. The residue is an ethereal extract. It is precipitated fairly well by means of the iodized iodine and molybdophospate of soda reagent.

Indirect demonstration will be given if we find in the products of excretion those poisons which we have observed in the tissues and in the intestinal canal; and, if it is proved that these poisons are eliminated by organs in which they are not formed, the logical conclusion will be that the blood is the necessary medium between the seat of the formation of these poisons and their place of elimination. But the poisons which exist in the tissues and in the intestinal canal are also found in the urine, either naturally or modified by oxidation or united to nitrogenous or sulphur radicals: oxalic acid, in the state of oxaluric acid; phenic acid, in the state of compound sulphophenic acid, or phenyl-sulphurous; bodies of the aromatic series,—indol, skatol, cresol; butyric acid, as in the stomach; lactic acid, as in the stomach and first part of the intestine; acetic acid, as it is formed under certain pathological influences, in considerable quantity in the whole length of the intestinal canal.

We also find alkaloids in the urine: some show themselves in a modified form, as quinine; others naturally, and without having undergone any previous alteration. Among these alkaloids some are soluble in chloroform, others are insoluble in this body, but soluble in ether; both are found in the urine, with the same characters as in the intestine. There is nothing in physiology which warrants us in considering all these bodies as products elaborated by the kidney; it is the blood which carries them there. One of the first authors occupied in the experimental investigation of these intoxications (Stich) thought that the poisons of the intestinal canal must be neutralized, destroyed, or undergo modifications which would deprive them of their toxicity, consequent upon their passage through the absorbent membranes of the intestinal canal, which played the part of a dialyzer, through the epithelial cells and through the walls of the capillaries. He is astonished to find so many poisons in the intestinal canal and yet so few toxic accidents; and, considering that the poisons of the intestinal canal are innocuous to the animal which has formed them, while the same poisons become harmful to an animal of any other species into which they have been introduced by the rectum or stomach, he is led to think that each kind of animal has the power of destroying of itself the poisonous substances which it forms. This is a view of the matter of which we have no demonstration.

According to Hoffmeister, the leucocytes play a part in the transformation of peptones into albumin, since we no longer find in the emunctories the peptones which we have injected into the blood. We could, perhaps, apply this hypothesis of Hoffmeister to the destruction of poisons, and say that the toxic substances coming from the intestinal canal are neutralized in the blood by the leucocytes. To explain the harmlessness of the poisons of the intestinal canal we have in addition invoked the protective action of the liver. This organ stops, arrests, as we know, certain portions of our food; it impedes the passage of grape-sugar and stores up glucose under the form of glycogen. It plays also a protective part in arresting alkaloidal substances. Heeger has injected into the portal vein blood containing alkaloids (nicotine, strychnine, morphine, quinine). The blood examined coming from the liver contains less of these; the substances injected have diminished by one-fourth or one-half. Perhaps the liver places itself in opposition to all the poisons of the organism, and robs it of the blood which carries them.

Schiff has revived the question. He operates with nicotine. The same dose of this substance which, introduced into a peripheral vein, kills an animal, does not kill another animal of the same weight if we inject it into a branch of the portal vein. Schiff introduces a quantity of nicotine into the intestinal canal of an uninjured animal, and it is not found to be intoxicated by it. The same dose poisons the animal if we have ligatured its portal vein, for then the toxic substance reaches the general circulation by the accessories of the portal venous system, without having passed through the liver, which would have arrested it.

Fresh liver is triturated with nicotine. An infusion of this is injected into an animal, and it does not kill it. The same dose of nicotine ground up with an equal weight of renal or muscular tissue kills it. The liver is not alone content in arresting these poisons; it destroys them. These facts have been experimentally verified in my laboratory by C. H. Roger, who, as regards this question of the protection of the organs by the liver, has added to our knowledge many new facts, which I shall have occasion to describe to you. But the alkaloids are not the most poisonous substances of the organism. This explanation is right as regards them, but is not applicable to all; it is necessary to add to it this other piece of information,—that man escapes intoxication by the activity of the intestinal, cutaneous, pulmonary, and renal emunctories.

The part played by the intestinal emunctory in the elimination of certain poisonous substances is attested by the commonly fetid stools of persons who frequent the postmortem theater. Their fetid character recalls the putrid odor of the emanations from the cadavera.[1] Sometimes this emunction is defective, for, if the largest part of the toxic material is thus expelled, yet some is absorbed; there is a defective circle for certain molecules of poisons. We find in the intestine toxic substances arising from the disassimilation of such organic matter as taurocholic and glycocholic acids, or their derivatives, cholic and cholalic acids, and dyslysin, a body formed by the liver, afterward transformed in the intestine. We find mineral salts formed out of bile or secreted by the intestinal glands themselves. The intestine also contains gases which are not all formed there; there are individuals in whom, in a very short time, an excessive tympanitis is developed. In such cases certain gases are probably secreted by the digestive canal. I do not know what they are, nor even whether they are analogous to those which bring about fermentation. We find hydrocarbons, sure enough; nitrogen probably;

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[1] I have known medical men and students who could not attend an autopsy in the postmortem theater of an infirmary without suffering from diarrhœa.—T. O.

perhaps carbonic acid, and even oxygen, since certain aërobic microbes live in the intestine. To what extent are these gases poisonous? It is difficult to reply to this question. Those which produce hysterical tympanitis do not appear to be poisonous.

From these facts follow certain applications that may be made to pathology. Has it not been said now for a long time past that there are "salutary diarrhœas"? People who have lived for several years the subjects of diarrhœa, and retaining the appearance of perfect health, have seen their diarrhœa and their health disappear at one and the same time. We may derive from these facts some encouragement in inducing diarrhœa in certain cases, without, however, raising exaggerated hopes in anyone, the subject of a supplementary diarrhœa, of his being able to compensate the insufficiency by another emunctory. We have spoken of the intestine acting vicariously for the kidney by discharges of serum. For my part, I scarcely believe in vicarious functions any more for the skin than for the intestine. In increasing more actively the cutaneous and intestinal secretions we remove a considerable quantity of water from the organism, but not what ought to be eliminated dissolved in the water. There is a certain quantity of material associated with a determined quantity of water, according to the emunctory by which the water is thrown out. If, for example, there is in the blood 0.15 gram of urea for 1000 grams of water, the urine carries away 15 grams of urea for every 1000. The sweat will only carry away 0.15 gram for every 1000, exactly the proportion which is found, not in the blood, but in the liquor sanguinis. Then 1 kilogram[1] of water, which by the renal channel would have carried away 15 grams of urea, only carries away 30 centigrams by the skin and the intestine. One emunctory can scarcely vicariate for another.

By the skin are eliminated water, salts in small quantity, carbonic acid, and some volatile fatty acids. Copious perspirations may be useful in certain intoxications,—caused by poisons, for instance,—not because they eliminate the poisons themselves, but probably because they expel from the organism the abnormal products which it has formed under the influence of the poisons.

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[1] 1 Kilogram = 1000 grams = 15432.4 grains = about 2 lbs. 3 $^{1}/_{4}$ oz.
500 grams = 7716.2 grains = about 1 lb. 1 $^{5}/_{8}$ oz.
100 grams = 1543.2 grains = about 3 $^{1}/_{2}$ oz.
25 grams = 385.8 grains = about $^{7}/_{8}$ oz.
5 grams = 77.2 grains = about $^{1}/_{6}$ oz.
$\left.\begin{array}{l}1\text{ gram or}\\ 1000\text{ milligrams}\end{array}\right\} = 15.4$ grains

In many putrid intoxications in individuals who are the subjects of deep-seated, foul sores the odor of the skin recalls that of their suppuration. What enables us to understand the useful part played by perspiration in the cure of these morbid states is the odor which the skin assumes under the influence of certain disorders of nutrition. Among hypochondriacs—the alienated, living in absolute inactivity, and with defective alimentation—fatty acids are eliminated more abundantly by the skin. From this arises the odor special to the places inhabited by men forced to this kind of life,—the odors of asylums, of prisons, barracks,—odors which differ one from the other. [So marked is the odor that, since it clings to newly washed clothes, laundresses can name the patients to whom the clothes belong by their peculiar smell.] When nutrition is deranged, by depressing influences acting through the intermediary of the nervous system, we may be warned of its being so by the odor.

There is in existence an experimental demonstration of the part which the cutaneous emunctory plays in the elimination of toxic substances. We know that the varnishing of the skin of animals produces a marked fall in the heat of the body. Is this the result of failure of the cutaneous respiration? It is hardly probable. Is it due to the action of the varnish upon the nerve terminations? Why, this reflex action is much less than faradization, the application of cold or of heat; besides, what these forms of irritation of the tissues determine is albuminuria, not hæmaturia, convulsions, and reduced temperature. What is special to the varnishing is perhaps the retention of poisonous substances which the skin ought to eliminate.

By the lungs are eliminated carbonic acid (1100 grams in twenty-four hours), water, ammonia sometimes, and often volatile fatty acids, which explain the fetid character of the breath of people the subjects of constipation and of hypochondriasis, and which are the result of a depraved nutrition or of an incomplete destruction of matter. By the lungs, too, are eliminated poisonous substances scarcely known, to which du Bois-Reymond has drawn attention, especially the volatile poisons accidentally introduced into the digestive canal (alcohols, ethers, chloroform, asafœtida).

But of all the organs of elimination the most important is the kidney. One cannot, as in the case of the intestine, reproach it with being a defective emunctory, capable of reabsorbing a part of the products which it eliminates. Absorption does not take place in the urinary channels, at least in the normal condition. If there is produced a desquamation of epithelium, intoxication, it is true, shows itself; it is then a complex thing, resulting not only from the reabsorption of substances which the kidney ought normally to eliminate, but from poisonous substances which the decomposing urine forms in the urinary channels under the influence of ferments which are found there.

What, then, does the kidney eliminate? Everything save gaseous material: in the first place, water; then two-thirds, at least, of the solid matter, especially mineral matter, of which you will not be slow in recognizing the eminently poisonous power; many nitrogenous substances (urea, coloring and odoriferous material). Certainly all these substances are not poisonous, but many of them are. What is certain is that urine, taken altogether, is toxic. We have always regarded oliguria as a serious thing, whereas, on the contrary, at the declination of fevers a critical polyuria is nearly always useful, because it expels poisonous substances formed by the economy during the illness. There may arise unpleasant symptoms, according to the relative impermeability of the kidney for certain substances.

[Beyond regulating the temperature of the body, and therefore acting in a purely physical manner, we know little of the chemical composition of perspiration. The question has sometimes been asked to what extent is sweat toxic? Rohrig and Aquierolo believes that it has very few toxic properties, while Arloing is of opinion that the injection of 15 to 30 cubic centimeters of sweat will kill an ordinary sized rabbit. Mavrojanis, who carried out a series of experiments, found that the toxicity of sweat varied according to muscular exertion and the amount and character of the liquids taken, but that under all circumstances it had a feeble toxicity. It required, on an average, 110 to 140 cubic centimeters for every 55 to 75 kilograms of living tissue. Death was never immediate; it never occurred until from twelve to thirty hours after the injection. The principal effects observed were a fall of temperature and hæmoglobinuria. Cabitto injected the perspiration of epileptics after convulsive attacks and found that it killed animals in doses of from 15 to 20 cubic centimeters. During the course of certain infectious diseases, notably small-pox, Quierolo noticed that the toxicity of sweat increased. This, too, occurred in malaria. As regards perspiration, there is always the probability that the discharge contains numerous microbes the influence of which must not be underrated when this liquid is injected into animals. Perspiration contains from 990 to 995 parts of water per 1000 and urine from 956 to 960. Charrin ("Les Défenses Naturelles de l'Organisms") remarks that, while fatal accidents are induced after injecting from 40 to 50 cubic centimeters of urine per kilogram of animal, it requires 70 of sweat, and even with this quantity death does not occur until several hours afterward. A liter of liquid leaving the human body by the kidneys carries an amount of poison capable of killing 20,000 grams of living matter, while the same quantity of liquid escaping by the skin only destroys, and that slowly, 14,000 grams.]

# LECTURE III.

## PRELIMINARIES TO THE EXPERIMENTAL STUDY OF THE TOXICITY OF THE PRODUCTS OF EMUNCTION.

**Necessity of demonstrating experimentally that the retention of excrementitious material may cause intoxication. Pulmonary, intestinal, and cutaneous emunctories are inconvenient for this demonstration. Choice of the urinary secretion for research upon the toxicity of the products of emunction.——Comparison of the various methods employed by the experimenter for introducing into the organism substances the toxicity of which he wishes to study. Introduction by the digestive canal and subcutaneous injection inconvenient. Advantages of intravenous injection. Its harmlessness; its facility. Uniformity of the results obtained.——Study of the action consequent upon the liquids employed to serve as excipients in the injection of poisonous substances,—water, alcohol, glycerin.**

THERE exists, as we have said, in the organism an incessant tendency to toxæmia from accumulation, and from which it escapes by various means, thanks to the part played by the liver, which forms an active barrier to poisons absorbed from the digestive canal, but is insufficient for those formed in the tissues,—thanks especially to the safeguard which is established through the emunctory apparatus. In order that intoxication may be avoided, it is necessary that the five emunctory offices should be in a state of anatomical and functional integrity; that the blood, the circulatory apparatus, and the nervous system should functionate normally. Everything caught in the meshes of these organs may cause intoxication. It seems, at least, that this should be so; but appearance may not be real: presumption is not demonstration.

If I say that death nearly always arises from intoxication,—because, in nearly all diseases, it is asphyxia which puts a termination to all vital acts, and that asphyxia is an intoxication,—I seem to be formulating a syllogism which is indisputable. Yet it is only a sophism, however, for asphyxia is a complicated thing, and if intoxication from excess of carbonic acid is one of its factors want of oxygen is another. There is, then, no fact so reasonable as that which requires demonstration. Consequently, we ought to prove that the retention of substances destined to be eliminated by the emunctories is capable of producing intoxication in the doses in which these substances are formed in the normal organism. The problem to be solved is to seek for the measure of the activity of the toxic substances which are eliminated in twenty-four hours by all the emunctories combined,—and what enables us to determine this in a given time is the quantity of poison capable of intoxicating a known weight of living matter. We cannot set ourselves to solve this problem with any emunctory that we choose.

Thus, among emunctories whose failure to functionate can contribute to intoxication of the organism the lung is beyond all dispute: without counting the other toxic substances it eliminates, the carbonic acid which it exhales in twenty-four hours would poison a man a great number of times.

The intestine does not offer a soil for useful experiments, for we are powerless to make the distinction between toxic products which are brought there by the secretions and those which are formed therein. In regard to the skin, researches are embarrassing, on account of the small quantity of products secreted and of the difficulty which we have of collecting them. It is, therefore, from the urinary tract that we will seek for the demonstration of the toxicity of the products of emunction; by it is reserved the speciality of eliminating toxic substances which are not volatile, a deduction being allowed for that which is destroyed in the liver and in the totality of the organism.

What methods are allowed to us for the introduction into the organism of toxic substances? Ingestion by the digestive canal is an illusory method. We are obliged to dilute the toxic materials to make them acceptable. We introduce them into an organ which is continually eliminating by the stools a part of its contents. How can we know what quantity of that which we have introduced has been absorbed? Besides, absorption from the intestinal canal is very slow, and the organism has time to protect itself by eliminating the poison. M. Morel-Lavallée has communicated to the Clinical Society the following fact: In a patient who had ingested 60 grams of laudanum from 2 o'clock in the morning to 8 o'clock in the morning, washing out of the stomach removed 45 grams of the poison. In six hours one-fourth only of the poison had been absorbed. When we proceed to the introduction of toxic substances by means of the digestive canal we never can know if what has been introduced has been absorbed, and we run the risk of being forced to consider substances inoffensive which are really poisonous.

Injection by the subcutaneous cellular tissue is liable, in great part, to be similarly criticised; elimination, it is true, will only be made by the blood, but absorption is slow, while emunction is rapid. It is, therefore, difficult to form an exact appreciation of the quantity of the injected substance which is contained in the blood at the precise moment at which such a phenomenon shows itself. Besides, the injection produces by itself certain disturbances which may cloak the action proper to the injected substance. It is painful, and provokes nervous reactions. It causes particularly albuminuria; the injection of 4 cubic centimeters of water by the subcutaneous method in the case of a rabbit induced this phenomenon.

There remains the intravenous channel. The dangers which were attributed to it at first are erroneous. It is almost as easy and quick from the operative point of view as injection into the cellular tissue; it is, besides, more searching, more inoffensive, and less painful. Thanks to it, we can, in a period equal to a complete revolution of the blood, distribute through the whole of the organism a known quantity of poisonous material, and know exactly what dose is contained in the blood at the moment in which there bursts forth the first indication of toxicity.

I have made comparisons between injections of saccharified urine into the intravenous channels and subcutaneously. When this is introduced directly into the blood glycosuria shows itself three minutes after the beginning of the injection.

### INTRAVENOUS INJECTION OF DIABETIC URINE.

On the 11th of December, 1884, into a rabbit weighing 1645 grams we injected into the veins 133 cubic centimeters of urine containing traces of albumin and 60 grams of sugar to the liter. The urine is filtered and neutralized. The quantity of urine injected represents 4.85 grams of sugar for each kilogram of the animal and 63.05 grams for each kilogram of blood. At the 33d cubic centimeter, emission of urine already rich in sugar. Toward the 71st cubic centimeter, fresh emission of urine, richer in sugar than the first, and sufficiently albuminous. At the end of the injection, third emission of urine, still richer in sugar than the two preceding. The temperature, one hour after, stood at 36.4° C. (97.5° F.). An hour and a half after the injection the urine is found still to contain sugar.

December 12th. The urine contains a less quantity of sugar. Temperature, 40° C. (104° F.).

December 13th. Trace of sugar; no albumin.

December 23d. The animal is quite well.

The same quantity introduced by the cellular tissue does not produce glycosuria, because absorption is so slow that the blood destroys the sugar as it is absorbed, without giving it time to reach the kidney.

### SUBCUTANEOUS INJECTION OF DIABETIC URINE.

Sixty-five cubic centimeters of the same urine are injected into the cellular tissue of a rabbit weighing 1750 grams,—about, therefore, 2.2 grams of sugar for each kilogram of the animal. After the injection the urine of the rabbit does not contain sugar; it is albuminous.

December 12th. No sugar. Temperature, 40.1° C. (104.2° F.). In the evening the animal dies. At the autopsy, in the region in which the injection was made, one sees neither suppuration nor gangrene, but a reddish liquid, full of mobile organisms, round, very small, which one also finds in the liver, and which appear also to exist in the blood.

The intravenous method is the less harmful, much as this may appear paradoxical. One hundred grams of fluid injected into the blood are not followed by any accident. The same quantity of this fluid, purified, or even previously raised to a temperature of 100 degrees, if we inject it under the skin, causes the animal to die from septic accidents. It is possible that some of the infective agents derived from the intestinal tube or from without cause the appearance of something in the cellular tissue, modified by the presence of the injected fluid, which is capable of killing the animal, whereas, on the contrary, when we inject into the veins fluid even in appearance septic, a liquid rendered opalescent by the presence of bacteria, there may result from this no accident, or albuminuria at the most.

### INTRAVENOUS INJECTION OF URINE RENDERED OPALESCENT BY THE PRESENCE OF BACTERIA.

November 8, 1884. Urine of a patient the subject of arteriosclerosis. Quantity passed in twenty-four hours, 850 grams. This urine is albuminous; it contains moving microbes, in the form of rods, short and numerous enough. Neutralized, and slightly alkalinized and filtered, it is injected into the veins of a rabbit weighing 1580 grams. The quantity injected is 135 cubic centimeters in eleven minutes,—about 86 for each kilogram of the animal. The temperature of the rabbit before the injection was 40° C. (104° F.). It falls to 37.2° C. (99° F.) immediately after. Myosis shows itself slowly: it only appears toward the 80th cubic centimeter. There is emission of very little urine. After the injection the animal remains lying on its side; its respiration is slow. The reflexes are hardly perceptible. At the end of twenty minutes the temperature is 37.8° C. (100° F.); the animal is upon its paws.

It has lost 0.8 × 2.8 × 1580 calories = 3539 calories.
The urine has absorbed 12.2 × 0.135 calories = 1647 calories.

The rabbit, therefore, has made less by 1892 calories.

November 10th. The animal has traces of albumin.

November 15th. It is quite well.

Perhaps bacteria are, after a time, neutralized by the oxygen of the blood, especially if they are anaërobic bacteria, or if they are the common bacteria which have not yet exercised their influence except upon dead matter. We can inject thousands of millions of certain bacteria without the organism being the least disturbed by it.[1]

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[1] Watson Cheyne, in his "Lectures on Suppuration," delivered at the Royal College of Surgeons, London, February, 1888, has shown how the disease which is experimentally produced stands related to the number of micro-organisms injected. Taking cultivations of proteus vulgaris, for example, he found that $^{1}/_{10}$ cubic centimeter of an undiluted cultivation was rapidly fatal when injected into a rabbit,—the quantity injected contained 250,000,000 of bacteria; also, that 56,000,000 bacteria caused extensive abscess, the animal dying in from six to eight weeks. Fewer than 18,000,000 seldom produced any effect. In diseases of this nature, however, many things have to be considered,—not only the quantity injected, but the virulence of the micro-organisms and the susceptibility of the animal. Mice are peculiarly susceptible to

The process of intravenous injection is applicable to everything that is soluble except oxygen. Nevertheless, it has been proposed at the Academy of Sciences to make intravenous injections of oxygenized water. The splitting up of this, as I have observed, would be immediate, and would end in gaseous pulmonary embolism. At most, I have only seen experimental injections utilized as a method of study, and not their application to therapeutics. Intravenous injections of medicines into the bodies of men ought, according to the new order, only to be employed in cases altogether exceptional,—in cholera, for example,—or, as I have already once said, in a disease certain to be speedily fatal,—confirmed hydrophobia.

It remains for us, before proceeding with the injection of toxic substances, to study how liquids behave physiologically which serve for the dissolution of those substances. The only excipients employed are water, alcohol, and glycerin. In the rabbit, distilled water, at a temperature very notably below that of the blood, only commences to show itself toxic when we inject more than 90 cubic centimeters of it for each kilogram of the animal,—say, for 100 grams of blood 117 of water. Death ensues with 122 cubic centimeters for each kilogram of the animal; that is, 157 grams of water to 100 of blood. Absolute alcohol is toxic beyond 0.6 cubic centimeter for each kilogram of the animal. The clot which it produces immediately redissolves in the blood coming from other veins, and there arises no embolus from it. The more alcohol is diluted, the more we can inject of it. The degree of dilution the most favorable is 20 grams for each 100 by volume,—20 cubic centimeters of absolute alcohol for 80 cubic centimeters of water; 1.45 cubic centimeters of absolute alcohol carried to this degree of dilution produce

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septicæmia; the injection of a single bacillus has induced death, while 4 cubic centimeters of a jelly cultivation, and which contained myriads of bacilli, could be injected into the ear of a rabbit without causing more than slight constitutional disturbance and local redness with swelling, which lasted only a few days. In the case of staphylococcus pyogenes aureus, Cheyne showed (Brit. Med. Journal, March 10, 1888) that it was necessary to inject 1,000,000,000 cocci into the muscles of rabbits in order to cause a rapidly fatal result; 250,000,000 produced simply a small circumscribed abscess.—T. O.

narcosis and coma; 3 cubic centimeters kill. For each 100 grams of blood it is, then, necessary to take 2 cubic centimeters of alcohol to produce narcosis and 3.9 cubic centimeters to bring about death.

Glycerin is less toxic than alcohol. We cannot employ pure glycerin; it produces viscid emboli. We must prefer dilution of it to 50 for each 100. We establish that 5 cubic centimeters of anhydrous glycerin for each kilogram of the animal produce muscular tremors, and that 14 cubic centimeters induce death, with immediate cadaveric rigidity. We know, then, for the future, that the substance whose toxic power we wish to test by intravenous injection ought not to be dissolved in more than 90 cubic centimeters of water,—in more than 1.45 cubic centimeters of alcohol, diluted in the proportion of 20 to each 100, or 5 cubic centimeters of glycerin, diluted in the proportion of 50 to 100 for each kilogram of the animal.

# LECTURE IV.

## ON THE TOXICITY OF URINES.

**Admitted from all time by physicians, the toxicity of urine has only recently been demonstrated.——Cl. Bernard and Frerichs have stated the question. Isolated study of some of the toxic elements of certain urines: Gabriel Pouchet. Study of the toxicity of urine taken in its entirety—Negative conclusion: Muron. Positive conclusion: Feltz and Ritter, Bocchi and Schiffer. Study of certain pathological urines: Lépine, Dupard, and Guérin.——My own experiments upon the toxicity of normal urine injected *en masse* by intravenous channel. Reply to certain objections raised against this method. Choice of the rabbit as the animal to exhibit reactions.——Physiological phenomena consequent upon the intravenous injection of normal urine,—myosis, accelerated respiration, torpor, polyuria, fall of temperature due to diminished heat production; survival or death, according to the dose injected. Discussion upon the possible causes of death. Determination of the unity of toxicity. Urotoxy. Urotoxic coefficient. Toxicity of urines different according to whether they have been secreted during the waking hours or sleep.**

WE have said that if the organism forms poisons and yet is not poisoned, it is because the liver stops some of them and that the rest are eliminated. The safeguard to the economy resides in having an organ of arrest and in the emunctories. We have admitted this idea hypothetically, but we have recognized the necessity of verifying experimentally this view of the matter, reasonable as it appears to us. From among possible demonstrations we have chosen that which consists in proving that the emunctories really cast out externally toxic substances and that the excrementitous products are toxic. For various reasons, which we need not recall, we have addressed ourselves, in order to verify the toxicity of excrementitious products, to those which the kidney eliminates, and we have adopted the intravenous injection as the experimental method.

Are urines toxic? To this question we have at all times replied in the affirmative,—so much so that there is no necessity to raise the question again. Upon this undebated point has been built the theory of uræmia. Urine is toxic: thus, when it ceases to be secreted the organism is poisoned. We may say that this is a true medical opinion of the matter; but, true as it appears to be, it claims demonstration. Cl. Bernard raised the question; Frerichs has followed it up. Physicians and physiologists have, after these, emulously striven to find out what are the substances to which urine owes its toxicity,—ammonia, urea, etc. In all these researches it is not of the urine itself that there is question, but certain substances which we find in it or which are developed in it in consequence of catalytic changes,—carbonate of ammonia, for example. It is the study of certain toxic substances of the urine which we have at length broached, and not that of the toxicity of urine in kind. We have blamed the coloring matter, odorous and volatile, also mineral matters,—potass. in particular. These are, without doubt, toxic; but they constitute only a part of the toxicity of urines.

M. Gabriel Pouchet has found in normal urine alkaloids chemically similar to the toxic alkaloids. In 1882 I extracted from certain urines taken from patients the subjects of infectious diseases alkaloids, with which I have been able to produce, experimentally, dilatation of the pupil, acceleration of the beats of the heart,—physiological effects which approach those of atropine. But the question here was one of abnormal alkaloids, or at least of alkaloids extracted from the urines of sick people. It is by repeated attempts, made in various ways, that we approach the solution of the problem.

The question, taken in its entirety, dates from 1868.[1] Muron, having made subcutaneous injections of urine, affirms the nontoxicity of it; but the method which he adopted ought to put us into a state of mistrust; we have seen why. MM. Feltz and Ritter (in 1881) made intravenous injections of urine just as it is, and have concluded for the toxicity of urine. Bocchi

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[1] Experiments dealing with the injection of urine into the blood-vessels of animals began as far back as the early part of the nineteenth century. Vauquelin and Segalas (Journal de Physiol. Exper., Paris, 1822, tome ii, p. 354) in 1822 caused the death of animals by injecting urine into their veins. As their experiments were not conducted under proper precautions it is more than probable that the fatal result was due to septicæmia and not to the toxicity of the urine. Bichat and Courten are believed to have carried out a similar series of experiments before 1812.—T. O.

(at the end of 1882) repeated the experiments, and also concluded that urine is toxic, considered as a whole. He has subcutaneously injected normal urine into frogs, and has killed them; but in mammals—the rat and guinea-pig—he has not produced the toxic phenomena which he met with in the frog. In April, 1883, Schiffer employed ethereal extracts of urine. He killed frogs with the extract taken from 16 to 25 grams of urine, and rabbits with a quantity of extract which represents $1\,{}^1/_2$ liters of urine; but, if he has demonstrated the toxicity of a product contained in urine, he has not elucidated the problem of the toxicity of normal urine in man, for, according to these experiments, it would be necessary, while the due proportions were observed, that man should retain in his body a quantity of urine equal to his own weight in order to be intoxicated by it. The experiment of Schiffer only proves that urine contains something which, in an excessive dose, may become toxic. Very interesting experiments, regarded from a physiological point of view, were made in 1883 and 1884 by M. Dupard, under the inspiration of M. Lépine, and afterward by MM. Lépine and Guérin; but as these experimenters only made use of pathological urines, the results obtained do not demonstrate the toxicity of normal urines. It is necessary to return to the method suggested by Feltz and Ritter,—the injection of normal urine just as it is; that is what I have done, as these authors did in 1883 and 1884, by intravenous channels.

It seems at first sight unlikely that one could introduce into the vascular system urine as it is; and, before everything else, it is necessary to reply to certain objections which cannot fail to be raised against the legitimacy of this proceeding. And, first, can we, without causing accidents, introduce into the blood a considerable quantity of water, such as that which would serve as a vehicle for the solid matter of the urine? We said in the preceding lecture that we can inject without danger into the blood up to 90 cubic centimeters of water for each kilogram of the animal. Can we inject urine as it is with an acid reaction? Do we not run the risk of attributing to the action of urine effects which would be sufficiently determined by the introduction of a normally acid body into an alkaline medium? Theoretically we cannot afford to overlook this possible cause of error, although there may be reason for asking ourselves if it concerns the theory of intoxication by retention in the blood of urine not secreted, and if the acidity might not be due to the action only of the renal secretion. We see neutral salts which have become acid after having undergone dialysis; it is there a borrowed acid. In every case it would not be legitimate to compare the effects of the retention of neutral urine with the injection of acid urine. In fact, I have acknowledged that the question of the reaction is a thing of indifference. At first the urine is acid to a feeble degree; it contains few free acids; the acidity is chiefly due to acid salts. I have injected, for the sake of comparison, and without obtaining differences in the results, acid urines and the same urines exactly neutralized by carbonate of soda. Yet, to be more cautious, I have, in all my experiments, exactly neutralized the urines before injecting them into the blood. It is a precaution which cannot diminish the toxicity of urines, and which puts in the shade the objection announced higher up. That admitted, we cannot inject into the blood of an animal normal urine without determining physiological phenomena and death with doses generally less and often much inferior to those in which distilled water is toxic.

The phenomena which I am going to describe have been observed exclusively in the rabbit. The rabbit is the best animal to choose when there is question of injecting into the veins. The posterior marginal vein on the dorsal part of the face, as it spreads over the ear, easily allows of penetration taking place, without preliminary removal of the skin, by means of a Pravaz syringe. We can, even in the rabbit, penetrate directly into the median artery of the ear. The choice of this animal singularly diminishes the difficulties, and especially the slowness, of intravenous injections. The guinea-pig, which offers the same advantages, scarcely lends itself so well for experiments in the laboratory, for there are economical necessities before which it is necessary to bow.

The first phenomenon which follows the intravenous injection of normal urine is contraction of the pupil. After the injection of 10, 12, or 15 cubic centimeters of urine there appears a myosis, which goes on gradually increasing until the pupillary opening becomes pin-pointed. A little after the beginning of the injection we notice acceleration of respiratory movements, with a diminution of their range. Then the animal is enfeebled, its movements become irregular and laborious; somnolence now comes on. We remark, also, increase in the urinary secretion and frequency of voiding the urine. Urine increases more than any other material the urinary secretion. The diuresis induced by the injection of distilled water is not to be compared with that produced by the injection of normal urine. At the same time the temperature falls. This fall is constant, it is true, after every intravenous injection of liquid, but it is much more considerable after the injection of urine. The amount of heat lost by the animal is greater than that necessary to raise to the temperature of the blood the quantity of liquid injected. It is a thermic fall, which is dependent upon a diminution of heat production. The temperature of the rabbit falls from 39° C. (102.2° F.) or 37° C. (98.6° F.) to 32° C. (89.6° F.); the hypothermia of itself in certain cases may explain the death.

We also notice a diminution of the palpebral and corneal reflexes; often, too, exophthalmos. Death comes at last, without convulsion or with moderate muscular tremors, with persistence of the cardiac beats, and of contractility of the striated and unstriated muscular fiber. The pupil remains contracted after death; then it dilates again in some of the cases. If the smallest dose of urine is injected,—sufficient to produce coma, but not death,—the animal remains passive, with respiratory movements of feeble range; chilled; with pupillary contraction; and with a polyuria such that every two minutes an emission of urine takes place. The superficial vessels are dilated; the arteries beat with such amplitude that their pulsations are easily felt up to the tip of the ear. Then torpor diminishes, the fall of temperature is arrested, heat production goes on again, and the pupil dilates. At the end of half an hour return to health is definite, without secondary phenomena. The animal may be kept under observation for weeks or months, without our being able to observe in it any pathological accident. One fact to note is, that we rarely set up albuminuria unless, for the most part, an albuminuria which is very slight and very fleeting in the animals which survive. On the contrary, after the injection of pathological urines—certain kinds, at least—albuminuria is constant and notable; one may observe, too, hæmaturia.

What quantity of normal urine is necessary to produce intoxication by intravenous injection? This is a difficult question to decide. The oscillation habitually takes place between 30 and 60 cubic centimeters for each kilogram of the animal, —45 cubic centimeters, on an average. Pupillary contraction often begins to show itself after the employment of 10 cubic centimeters. The urine of a subject in whom abundant drinks had produced a normal polyuria has been injected with impunity up to 97 cubic centimeters for each kilogram of the animal,—a dose in which distilled water is already toxic. The urine of this same individual, who was submitted to a chill without becoming febrile, has killed with a dose of 12 cubic centimeters for each kilogram of the animal. The variations of toxicity, already large in the limits of the normal state, become still more considerable as we reach the border of the pathological.

Pathological urines are not always more toxic than normal urines; they may be less; they may differ from them in producing other symptoms. Certain pathological urines determine, with a dose of 10 cubic centimeters, convulsions, which we hardly ever observe after the injection of normal urines. With certain others it is necessary, in order to induce a phenomenon of some kind or other, to inject as much urine, and even more, than the dose in which distilled water causes death. Thus, disease sometimes augments, sometimes it diminishes, the toxicity of urine. In certain albuminurias the innocuous nature of the urine is a remarkable fact; the kidney seems to have separated from it the toxic substances, retaining them within the organism.

When death follows an injection of urine, we may suppose that it results from the mechanical action of the mass of urine injected or from dilution of the blood. It is not so; for we can double and almost treble the mass of blood without inconvenience. Nor is death more to be attributed to the general hydration of the body. If we reduce by evaporation the quantity of urine by one-half, only expelling the water from it, the toxicity is doubly increased. The degree of concentration of a healthy urine causes its toxicity to vary: a healthy man, but oliguric, is more toxic than the polyuric, so far as regards an equal quantity of urine, which proves that the urine does not kill by the water, but by the substances which are in a state of solution in the water. Whatever those substances may be, it is interesting to know the degree of toxicity that they communicate to urines; that is to say, the toxic power of the matter which is elaborated by a given weight of man and is eliminated in a given time by his urine.

It has appeared to me necessary, for the clearness of later explanations, to create a new name, and I excuse myself for doing so. This neologism has for its object the denomination of the unit, which will serve as a term of comparison in the estimation of the variations of the toxicity of urine. I shall call the unit of toxicity "urotoxy"; that is to say, the toxic amount necessary to kill a kilogram of living matter. This unit we shall determine by experiment. I shall study thus the urotoxic coefficients; that is to say, the quantity of urotoxies which 1 kilogram of man can form in twenty-four hours.

A healthy man, weighing 60 kilograms, passes in twenty-four hours 1200 cubic centimeters of urine. If 50 cubic centimeters of this urine kill 1 kilogram of animal, 1200 cubic centimeters ought to kill 24 kilograms of the animal; 60 kilograms of man make and eliminate therefore by the kidneys in twenty-four hours what would kill 24 kilograms of animal. Thus, 1 kilogram of man forms in twenty-four hours what would kill 400 grams of an animal. In order to kill 1 kilogram it is necessary to have 1 urotoxy. The urotoxic coefficient of this man of 60 kilograms is thus 0.4. This is almost the normal coefficient, which I have found to be, on an average, 0.464.

If 1 kilogram of man forms in twenty-four hours what is sufficient to kill 464 grams of animal, he forms in twenty-four hours almost one-half of what is necessary to kill himself. On an average of two days and four hours man makes a mass of urinary poison capable of intoxicating himself. There are variations in the normal state for the urotoxic coefficient, but they are limited. In the pathological state the urotoxic coefficient rarely exceeds 2 and rarely descends below 0.10.

The toxicity of normal urines varies according to numerous circumstances,—cerebral activity, muscular activity, sleep, diet, etc. The variations bear upon the intensity and upon the quality of this toxicity. The urines of sleep, although more dense,—more rich in solid matter,—are, in equal volumes, almost always less toxic than the urines of the day. In an equal time the urines secreted during sleep always contain an amount of material less toxic than that secreted during the day. Man elaborates during sleep from two to four times less poison than during an equal time of cerebral activity.

### TOXICITY OF THE URINES FORMED DURING THE DAY AND OF THOSE FORMED DURING SLEEP.

September 15, 1885. We gather the urine of twenty-four hours of a healthy adult man weighing 81 kilograms and 700 grams. These urines are collected in three portions coresponding to the periods of secretion, having in each a duration of eight hours. The first portion commences from the moment of waking—quarter past 7 in the morning—to quarter past 3 after midday (morning period); the second portion from quarter past 3 to quarter past 11 at night (evening); the third portion from quarter past 11 to quarter past 7 on the following morning (sleep).

*Urine of Eight Hours—the Morning Period.*—Quantity, 365 cubic centimeters; density, 1027. This acid urine is exactly neutralized by bicarbonate of soda, filtered, and injected into a vein of the ear of a rabbit weighing 1750 grams. The rectal temperature of the rabbit before the operation was 39.6° C. (103.2° F.); owing to its not moving about, the temperature fell at the beginning of the injection to 39.2°C. (102.6° F.). Contraction of the pupil began when the animal had received 25 cubic centimeters; at 33 cubic centimeters, emission of urine; at 35 cubic centimeters, restlessness, respiratory arrest, loss of palpebral and corneal reflexes; death. At this moment the temperature was at 39.3° C. (102.8° F.). The heart still continued to beat for some little time. The temperature of the urine injected was 26° C. (78.8° F.). The animal was killed by the injection of $\frac{35\times1000}{1750} = 20$ cubic centimeters of urine for each kilogram of the animal.

*Urine of the Eight Hours Belonging to the Evening Period.*—Quantity, 320 cubic centimeters; density, 1028; reaction, acid; neutralized and filtered; this urine is injected into the vein of a rabbit weighing 1560 grams. At the beginning of the injection the rectal temperature of this rabbit was 40° C. (104° F.). At 3 cubic centimeters, quickened respiration; at 28 cubic centimeters myosis commences, and is complete at 36 cubic centimeters; at 35 cubic centimeters, excessive movement; at 39 cubic centimeters, convulsions, opisthotonos, death. The heart continues to beat. The rectal temperture at the moment of death is 39.8° C. (103.6° F.). The temperature of the urine injected was 23° C. (73.4° F.). The animal was killed by the injection of $\frac{39\times1000}{1560}=25$ cubic centimeters of urine for each kilogram of animal.

*Urine of the Eight Hours of Sleep.*—Quantity, 220 cubic centimeters; density, 1031; reaction, acid. This urine, neutralized and filtered, was injected into a vein in the ear of a rabbit weighing 1600 grams. At the beginning of the injection the rectal temperature was 40.2° C. (104.5° F.). After 6 cubic centimeters had been injected there was quickened respiration. At 21 cubic centimeters myosis had begun; at 33 cubic centimeters, clonic convulsions; at 34 cubic centimeters, loss of palpebral reflexes, exophthalmos, and momentary suspension of respiration; at 46 cubic centimeters, very severe clonic convulsions; then opisthotonos and death. The heart continued to beat. The rectal temperature at the moment of death was 39.9° C. (103.8° F.). The temperature of the urine injected was 23° C. (73.4° F.). The animal was therefore killed by the injection of $\frac{46\times1000}{1600}=28.75$ cubic centimeters of urine for each kilogram of animal.

In equal volumes, the urines of the morning period, although less dense, are more toxic than the urines of the evening period. The totality of the urines of the morning period is represented by $\frac{365}{20}$ $= 18.25$ urotoxies. The totality of the urines of the evening period represents $\frac{320}{25} = 12.8$ urotoxies. The urines of the sixteen hours of day represent, therefore, 31.05 urotoxies; or, by the hour, 1.9406; or, by the hour and per kilogram of man who has furnished the urines, 0.02375. During one hour of wakefulness this man has therefore eliminated on an average per kilogram of his weight a quantity of urinary poison capable of destroying 23.75 grams of living tissue. In equal volumes, the urines of sleep, although more dense, are less toxic than the urines of wakefulness. The totality of the urines of eight hours of sleep represents 7.65217 urotoxies; or, by the hour, 0.956521; or, by the hour and per kilogram of the man who has furnished the urines, 0.0117 urotoxies. One kilogram of man, during one hour of sleep, eliminates, therefore, a quantity of urinary poison capable of destroying 11.7 grams of living tissue. In sixteen hours of wakefulness this person has eliminated per kilogram what would kill 380 grams of animal, and in eight hours of sleep he has eliminated what would kill 93.6 grams of ànimal. In the twenty-four hours (waking and sleeping) he has thus eliminated a quantity of urinary poison capable of destroying 437.6 grams of animal. The urotoxic coefficient of this man was therefore 0.4736. From this we conclude that, to kill 1 kilogram of living matter, it would have required for each kilogram of this man two days, two hours, and forty-three minutes.

On September 19, 1885, we gathered the urine of twenty-four hours of a healthy adult man weighing 81 kilograms, 700 grams. This urine had been received in two portions,—one corresponding to the sixteen hours of wakefulness and the other corresponding to the eight hours of sleep.

*Urine of Sixteen Hours of Wakefulness.*—Quantity, 700 cubic centimeters; density, 1028; urea, 24.4 grams for every 1000, or 17.08 grams for the whole of the wakeful period; reaction, slightly acid. This urine, neutralized and filtered, is injected into a vein of the ear of a rabbit weighing 1720 grams. The rectal temperature at the beginning of the injection was 40.3° C. (104.6° F.). At the time that 23 cubic centimeters of urine have been injected myosis commences; the pupil is pin-pointed at 33 cubic centimeters; at 36 cubic centimeters, exorbitism, agitation; at 43 cubic centimeters, respiratory pause; at 46 cubic centimeters, loss of eyelid and corneal reflexes, death without convulsions. The heart continued to beat. The pupils continued pin-pointed after death. The rectal temperature at the time of death was 39.5° C. (103.2° F.). The temperature of the urine injected was 22° C. (71.6° F.).

This animal has, therefore, been killed by the injection of $\frac{46 \times 1000}{1720} = 26.74$ cubic centimeters of urine for each kilogram.

*Urine of the Eight Hours of Sleep.*—Quantity, 225 cubic centimeters density, 1034; reaction, acid; urea, 27.2 grams for 1000, or, for the whole of the eight hours of sleep, 6.12 grams. This urine, neutralized and filtered, is injected into a vein in the ear of a rabbit weighing 1610 grams. The rectal temperature at the commencement of the injection was 40.2° C. (104.4° F.). Myosis commenced after 21 cubic centimeters had been injected; it was complete after 33 cubic centimeters; after 26 cubic centimeters, agitation; at 46, clonic convulsions; at 48, strong convulsions while in opisthotonos; death. The heart continued to beat but feebly, except the auricles, which contracted with force. The pupils remained contracted after death. The rectal temperature at the time of death was 39.7° C. (103.4° F.). The temperature of the urine injected was 22° C. (71.6° F.). This animal was, therefore, destroyed by the injection of $\frac{48 \times 1000}{1610} = 29.81$ cubic centimeters of urine for each kilogram. The urines of the sixteen hours of the wakeful period represent $\frac{700}{26.74} = 26.178$ urotoxies, or, by the hour, 1.6361;

or, by the hour and per kilogram of man who has furnished this urine, 0.2002. A kilogram of man in one hour of the wakeful state eliminates, therefore, what would kill 20.02 grams of living material.

The urines of the eight hours of sleep represent $\frac{225}{29\ 81} = 7.88336$ urotoxies, or, by the hour, 0.98542, and, by the hour and for each kilogram of body-weight of the man who has furnished the urine, 0.01206. A kilogram of this man in one hour of sleep eliminates, therefore, what would kill 12.06 grams of living tissue. There results from this that he eliminates what would kill, in sixteen hours of the wakeful period, 320.32 grams, and in eight hours of sleep, 96.48 grams of animal. Therefore, in twenty-four hours he eliminates what would kill 416.80 grams of living matter. The urotoxic coefficient of this man is beyond 0.4168. It would require for each kilogram of this man, in order to kill 1 kilogram of living matter, two days, nine hours, and thirty-five minutes.

During wakefulness the greatest toxicity belongs to the first half of the day period. From a very healthy adult I have gathered separately the urines of the three periods of eight hours, representing the whole supply of a day of twenty-four hours, waking and sleeping. The first two periods—from 7.15 A.M. to 3.15 P.M., and from 3.15 to 11.15 P.M.—represent the period of wakefulness. The last period—from 11.15 P.M. to 7.15 on the following morning—had been devoted to sleep. This man furnished, per kilogram and for every hour, in the first period (morning), what would kill 27.92 grams of living tissue; in the second period (evening) what would kill 19.58 grams; and in the third period (sleep) what would kill 11.70 grams. The proportion of the urinary toxicity during these three periods of the day has always been sensibly shown to be the same; it may be expressed respectively by the indices 7, 5, 3.

We observe that the minimum of this elimination of poison is at the moment when man is asleep; that it is then nine times less intense than the eight hours previously, in the middle of the period of wakefulness, and five times less than eight hours later on, at the end of the period of sleep. We see that from the minimum to the maximum, during the sixteen hours which represent sleep and the morning period of wakefulness, the intensity of the toxic elimination is produced with a rapidity twice greater. The urines of the day period do not only differ from the urines of sleep by a toxicity twice greater, but the toxicity of these two urines presents differences of a qualitative character. The urines of sleep are always markedly convulsive; those of the day period are very little or not at all convulsive, but they produce narcosis. It is at such a point that we are asked if there is no possibility of accepting the old toxic theory of sleep,—that, according to which, the activity of nerve-tissue is accompanied by the production of a substance from disassimilation, whose action upon nerve cells would be soporific. If this theory could be revived it would be necessary, I believe, to expand it, and to attribute to the whole of the economy the production of narcotic material. What is certain is, that during the day the body forms a substance which, when accumulated, induces sleep, and that during sleep it elaborates, instead of this narcotic substance, a convulsive substance which, when accumulated, produces muscular twitchings and induces waking.

The poisons of the day period and the poisons of sleep are not only different as regards intensity and quality, they are antagonistic: the one is the antidote of the other. If we mix the urines of the day period and those of the night proportionately to their respective bulks, the toxicity of the mixture is not a mean—it is not necessarily intermediate—between the toxicity of the urines of the day and those of sleep; it may be less than the mean of those urines which were the least toxic. From this we know that, in order to appreciate the whole of the toxic matter formed by man,—in order to determine his urotoxic coefficient,—it is well not to attempt the toxicity of his urines by employing a portion only of the mixture of the urines passed in the twenty-four hours. It is necessary to determine respectively the whole toxicity of the urines of the day period and the whole toxicity of the urines of sleep, then to add the two results. In determining alone the toxicity of the mixture of the two urines we would get too small an index.

### TOXICITY OF THE URINES OF THE DAY AND NIGHT MIXED.

We gathered the urine of twenty-four hours passed by a young, healthy man, aged 28, weighing 69 kilograms. We gathered separately the urine of nine hours of sleep—from 10 o'clock at night to 7 o'clock in the morning—and the urine of fifteen hours of wakefulness,—from 7 o'clock in the morning to 10 o'clock at night.

*Urine of Sleep.*—Quantity, 450 cubic centimeters; density, 1024. This urine, neutralized and filtered, was injected into a vein in the ear of a rabbit weighing 1775 grams. Death supervened, after very slight convulsions, when 91 cubic centimeters had been injected. The animal had thus received for each kilogram 51.26 cubic centimeters of urine.

*Urine of the Day Period.*—Quantity, 720 cubic centimeters; density, 1014. This urine, neutralized and filtered, was injected into a vein in the ear of a rabbit weighing 1725 grams. Death supervened, without convulsions, after 45 cubic centimeters. The animal had thus received 26.08 cubic centimeters of urine for each kilogram.

*Urine of Twenty-four Hours*—We mixed one-third of the urine of sleep (150 cubic centimeters) and one-third of the urine of the day period (240 cubic centimeters). This mixture represented pretty accurately the mixture of the urine of twenty-four hours. This urine, neutralized and filtered, was injected into a vein in the ear of a rabbit weighing 1555 grams. Death supervened, without convulsions, after 73 cubic centimeters. The animal had thus received for each kilogram 46.94 cubic centimeters. The urine of sleep represented $\frac{450}{51.26} = 8.776$ urotoxies. The urine passed during the day represented $\frac{720}{26.08} = 27.607$ urotoxies. The urine of the twenty-four hours represented, therefore, $8.778 + 27.607 = 36.385$ urotoxies; but if we wished to estimate this toxicity of the urine of the twenty-four hours by the experiment which shows the toxicity of the mixture, we find that this toxicity would only be $\frac{450\ 720}{46.94} = 24.925$ urotoxies. Thus, from the fact of their being mixed, the urines of the day and of night lose about one-third of their toxicity. From this we ought strongly to conclude that man eliminates during sleep urine which is partly antidotal to the urine of the day, or *vice versa*. There would thus be, therefore, in the different conditions of nerve function, different elaborations of material capable of giving rise to poisons antagonistic to each other. From this experiment we can equally deduce that this man was eliminating for each kilogram of his own weight, every hour during sleep, sufficient to kill 14.135 grams of living matter, and during the day 26.673 grams; that during the period of twenty-four hours (day and night) he was eliminating sufficient urinary poison to kill 527 grams of living matter. His urotoxic coefficient was therefore 0.527. To intoxicate his weight of living material he would require forty-five hours and twenty-eight minutes.

The toxicity of the urine of sleep being only half of the toxicity of the urine secreted during an equal period of the day, we might think that the urine of repose ought to be less toxic than the urine of muscular effort. But it is the contrary which is true. One day of great muscular activity, spent in the open air, in the country, diminishes the toxicity of the twenty-four hours by one-third, and on that day the toxicity does not diminish only during the time devoted to muscular exercise. The toxicity, which diminishes during work, remains less during the repose which follows this work and during the sleep which succeeds this day of muscular activity. This fact has, I think, an important bearing,—it shows that a large part of the toxicity is not attributable to the mineral substances, which certainly are not diminished by the fact of exercise, and that it depends upon organic substances incompletely oxidized, whose toxicity diminishes in proportion as oxidation is more completely effected. We urge upon all, without insisting upon it too much, the interest which this experiment has from a therapeutical point of view.

### INFLUENCE OF EXERCISE UPON THE TOXICITY OF URINE.

We gathered the urine of the day and of sleep of a man of 81.7 kilograms, after a day of great bodily exercise, spent in the open air. We have for the day urine 1070 cubic centimeters (density, 1020) and for the urine of sleep 243 cubic centimeters (density, 1027). These urines are acid. The urines of the day period were gathered on the 11th of October, from 1.15 to 10.30 in the evening, and on the 12th of October, from 7 A.M. to 1.15 P.M. We have therefore the urine secreted during fifteen and a half hours. The urines of sleep were received from 10.30 P.M. to 7 A.M., *i.e.*, during eight and a half hours.

Into a rabbit weighing 1360 grams we made an intravenous injection of the urine of the day period. Death supervened after 72 cubic centimeters, preceded by some slight convulsive movements. It had received, for each kilogram of its own weight, 52.94 cubic centimeters. The pupils were pin-pointed at the moment of death.

Into a rabbit weighing 1360 grams we injected the urine of sleep. Death occurred after 66 cubic centimeters, after severe convulsions and retroflexion of the body in the form of opisthotonos. It had received, for each kilogram of its weight, 49.26 grams. The pupils were pin-pointed.

Thus, during the fifteen hours and a half of the day period 1070 cubic centimeters of urine had been secreted. This urine killed a kilogram of rabbit with a dose of 52.94 cubic centimeters. Man during the day has therefore secreted what would kill $\frac{1070}{52.94}$ kilograms, and for each kilogram of man and for every hour $\frac{1070}{52.79 \times 81.7 \times 15.5} = 0.01596$ kilograms. Therefore, during the day period 1 kilogram of man secreted in one hour what would kill 15.96 grams of rabbit. During the fifteen and one-half hours of the day 1 kilogram of man secretes what would kill 247.38 grams of rabbit.

During eight and one-half hours of sleep 243 cubic centimeters of urine had been secreted. This urine killed 1 kilogram of rabbit with a dose of 49.26 cubic centimeters. Man, during eight and one-half hours of sleep, killed $\frac{243}{49.26}$ kilograms, and in one hour $\frac{243}{49.26 \times 85}$; and 1 kilogram of man secreted during one hour of sleep what would kill $\frac{243}{49.26 \times 8.5 \times 81.7} = 7.103$ grams of rabbit. In eight hours and thirty minutes of sleep 1 kilogram of man secreted what would kill 60.38 grams of rabbit. In twenty-four hours (night and day) 1 kilogram of man secreted sufficient to kill $247.38 + 60.38 = 307.76$ grams of rabbit.

The urotoxic coefficient of this man is, in round figures, 0.308; 1 kilogram of man, in order to secrete what would kill 1 kilogram, requires three days, five hours, and fifty-five minutes.

In equal time the urines of the day period have a toxicity more than double that of the urines of sleep. The exact relationship for the toxicity of sleep compared with the toxicity of the wakeful period is $7.103 : 15.96 = 0.45$.

On the whole, therefore, the urotoxic coefficient of this man, on a day of heavy muscular work in the open air, is 0.308. It was, at two periods of repose,—the 17th of September and the 19th of September,—0.474 and 0.417, or a mean of 0.445. The relationship of the toxicity of the man who works to the toxicity of the man in repose is as $0.308 : 0.445 = 0.692$, or, in round figures, 0.7. Muscular effort in the open air has therefore suppressed $^3/_{10}$ of the toxicity. In this man twice, on the occasion of sedentary work in town, the toxicity for each kilogram and for every hour had been, during the day, 23.75 grams and 20.62 grams,—a mean of 21.88 grams,—and during sleep 11.70 grams and 12.06 grams,—a mean of 11.88 grams. By the fact of severe bodily exercise in the open air it became, during the day, 15.96 grams and during sleep 7.10 grams. The amount $\frac{15.96}{21.88} = 0.729$. The amount $\frac{7.10}{11.88} = 0.597$.

Muscular effort in the open air diminished thus from 27 for every 100 the toxicity of the day, and its influence extended also to the period of sleep which followed work, causing a loss of 40 per cent. in the toxicity of the urine of sleep. The causes which influence urinary toxicity may therefore act during the period of their application and

**also during a long period of time after they have ceased to exist. It is for this reason, doubtless, that the morning period is more toxic than that of sleep and the period of sleep less toxic than that of the evening.**

It is not sufficient to know that the urines have been rendered toxic by the solid substances which they contain. What are these substances? Amid the different symptoms of urinary intoxication, what symptoms belong to such and such a substance? Is there no substance whose toxicity is masked by its union with those that are more toxic, these killing the animal before the first may even have been manifested, and whose toxic power would be shown if they acted separately? Is there not, in the pathological state, a diminution of normal toxic substances and an increase of other substances incapable normally of intoxicating? There are many other questions also to which we must endeavor to reply.

Before demonstrating the degree of the toxicity of urine taken in the bulk there is only one resting place for our researches. It is necessary to dissect, so to speak, this mass, and to operate upon it in portions, in order to know intimately the degree of toxicity of each of the elements which compose it.

# LECTURE V.

## CAUSES OF THE TOXICITY OF URINE.

***Résumé*** **of the physiological phenomena produced by the intravenous injection of normal urine. Definition of urotoxy and the urotoxic coefficient.——Research as to the possible causes of the toxicity of urine. Modification of the toxicity of urine by time, temperature, exposure to air, fermentation.——Examination of the constituent elements of urine from the point of view of the part which they may play in its toxicity. Water. Volatile substances. Urea: Intravenous injection of urea. Experiments of MM. Gréhant and Quinquaud by subcutaneous injection. Insignificant toxicity of urea. Uric acid: Intravenous injection of uric acid. Feeble toxicity of uric acid. Creatinin: Its toxicity *nil* (Ranke and Schiffer). Odorous substances. Coloring matters. Intravenous injection of colored urine and of urine decolored by means of carbon. Very important diminution of toxicity and loss of the myotic power of urine after decoloration. Alkaloids.——Analysis of the toxic properties of urine by the dichotomic study of the extracts. Substances soluble in alcohol. Substances insoluble in alcohol. Unequal toxicity and toxic modality different in the two extracts.——Effects produced by the substances soluble in alcohol,—somnolence, coma, diuresis, salivation. Hypothesis relative to the appearance of this property, which is not possessed by urine naturally.——Effects of the substances insoluble in alcohol. Convulsions, myosis, diminution of heat production. Unequal assimilation of the toxic power of urine to that of certain alkaloids.——Hypothesis bearing upon the explanation of the physiological effects proper to urinary extracts. Urea is, perhaps, the cause of the diuresis. Loss of the myotic power and considerable diminution of the curative property after carbonization, which has left in the urinary extracts nothing else than mineral matter.——Insufficiency of soda to produce the toxicity of urine. Toxic importance of potass, which partly contributes to the convulsive power of urine.**

HAVING introduced normal urine into the veins, I have been able to demonstrate that its toxic action bears especially upon the nervous system, since it paralyzes movement without destroying the contractility of muscle, in so far as it allows the heart to continue beating. Disorders of movement become, at length, apparent in the pupil, which becomes pin-pointed. Myosis persists up to death, without there being any lesion of the muscles of the iris, since the pupil generally dilates after death. The movements of the respiratory muscles are quickened, those of the locomotor muscles weakened. The loss of the reflexes in the advanced phases of intoxication, somnolence, and coma still show that the brunt is borne by the nervous system. It is in the same sense that the disturbances of the secretory apparatus are to be considered,—the frequent emission of urine, the salivary hypersecretion, of which we shall speak soon, and, last, the fall of the temperature by diminution of heat production. That is the first fact, and it is the fundamental one in the phenomena of intoxication.

Before going further, it is necessary to establish a standard to estimate whether one individual forms in a given time more toxic matter than another. I have adopted the term urotoxy,—toxic unit, or toxicity, of urines. The toxic unit is the quantity of toxic matter capable of killing one kilogram of living animal. In order to study afterward the reports of the various toxicities, I have established what the urotoxic coefficient is, of which a brief argument will explain the necessity.

If to kill a kilogram of rabbit 30 cubic centimeters of the urine of Peter and 60 cubic centimeters of the urine of Paul are necessary, we are first led to believe that the urine of Peter is the more toxic. Yet, we are not altogether right in stating the conclusion thus: for if, in twenty-four hours, Paul has secreted twice as much urine as Peter, the toxicity is equal in the two. I go further: Two individuals eliminate in twenty-four hours the same quantity of urine; they kill with the same dose a kilogram of rabbit; it does not necessarily follow from this that they have the same toxic power, for another cause of variation may intervene,—the weight of the individuals; if one, weighing less by a half than the other, makes the same quantity of toxic material, he has evidently a toxic power double that of the other.

We are thus led to define the *coefficient of toxicity as the quantity of toxic matter which a unit of weight produces in a unit of time.* I will say, with greater precision, *the urotoxic coefficient of an individual is the number of urotoxies* formed in twenty-four hours by a kilogram of that individual.

These premises granted, we come now to seek among the constituent elements of urine for those to which the toxicity of urine is due. We discard at once the idea that the water is toxic. It may be introduced with impunity into the blood in doses much larger than that in which urine kills. Besides, evaporation causes the urine to become more toxic. When, by evaporation, we reduce to one-half of its volume a urine which kills 1 kilogram of rabbit with a dose of 60 cubic centimeters, we see that this urine thus concentrated kills with a dose of 30 cubic centimeters. Toxicity depends, therefore, not on the water, but upon the substances which it holds in solution. If evaporation is made slowly, we notice an absolute increase of the toxicity, and no longer an increase proportional to the degree of concentration. This can only be explained by chemical changes undergone by substances that are unstable,—substances which really do not belong to the group of minerals. This fact, the increase of toxicity by evaporation, allows us also to conclude that the other volatile substances contained in the urine are not either the cause of its toxicity.

We increase the toxicity of urines by leaving them for a long time to themselves, even if we protect them from fermentation. Rise of temperature, exposure to air especially, length of time in keeping, all modify their toxic power. Such a urine which killed by coma becomes toxic with a smaller dose, but it does so by inducing convulsions. If fermentation is set up in it, the toxicity varies; it may be increased or diminished; it is in every case changed by it. If there is produced within it carbonate of ammonia, we may have the special phenomena witnessed in ammonæmia.

The increase of toxicity on keeping the urine already allows us to assume that it is not the mineral substances which are the sole cause of the toxicity, since they are not more abundant in old urine; the potass, notably, remains in the same quantity.

Before going further, we may pass in review some hypotheses which have been enunciated on this subject, viz.: the causes of the toxicity of urine. Formerly, for example, urea was considered the chief poisonous agent, after the teaching of Wilson. The intravenous injection of urea, which I have practiced a great many times, enables me to say that we can certainly kill with urea, as with many other bodies, by modifying the conditions of osmosis: by increasing in such proportions the density of the blood and the liquids of the organism we physically hinder the functions of nutrition. But the solutions of urea which have not this excessive density do not kill, or they lead to death

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only if we have injected more than 122 cubic centimeters for each kilogram,—a dose in which pure water kills.

### INTRAVENOUS INJECTION OF UREA WITHOUT MORBID PHENOMENA.

October 16, 1884. Into a rabbit weighing 1690 grams we inject, in ten minutes, into a vein in its ear, 100 cubic centimeters of an aqueous solution, which contains exactly 4 grams of urea. The animal has thus received per kilogram 2.366 grams of urea, and, as this urea has been introduced into its blood, that makes 30.758 grams per kilogram of blood,—about two hundred times the normal quantity ($2.366 \times 13 = 30.758$). The temperature at the commencement was 39.7° C. (103.4° F.); at the end of the experiment it was 38.8° C. (101.8° F.). No morbid phenomenon.

October 25th. The animal is well.

October 28th. It remains quite well.

The temperature of this animal has fallen in ten minutes nine-tenths of a degree. The heat capacity of the tissues being 0.8, the animal has, therefore, lost $1690 \times 0.8 \times 0.9 = 1216.8$ calories. On the other hand, water injected, which was, at the commencement, of a temperature of 16 degrees, is heated to 22.8 degrees, and consequently has absorbed $100 \times 22.8 = 2280$ calories. Water has, therefore, taken from the body of the animal a quantity of heat more considerable than that which it lost in falling from 39.7 degrees to 38.8 degrees. Consequently, the injection has not produced refrigeration by impeding heat production; on the contrary, there has been, during the period of the injection, an increase of calorification, since the temperature of the animal has remained higher than that which it would have attained by the fact alone of the refrigeration due to the injection.

Fatal accidents supervene only after an injection containing 6.31 grams of urea per each kilogram of the animal, or 82 grams per each kilogram of blood; a supposition that there is ten times more urea than we have found in the blood of patients who have succumbed, as one would say, to intoxication from this substance. It is not admissible that urea is the toxic agent of urine.

### INTRAVENOUS INJECTION OF A VERY LARGE DOSE OF UREA—DEATH.

October 25, 1884. We injected, in thirty-five minutes, into a vein in the ear of a rabbit weighing 1790 grams, 113 cubic centimeters of an aqueous solution of urea at $^1/_{10}$—let us say 11.3 grams of urea; or, for each kilogram, 6.31 grams; or, for the total mass of the blood (137 grams), 11.3 grams; or, for a kilogram of blood, 82.03 grams. After injecting 35 cubic centimeters, respiratory disturbances were the first to be noticed; respiration became slower. After 58 cubic centimeters, slight convulsions and tremors renewed from time to time; respiration was still further slowed. At the end of the injection the animal was comatose; it died ten minutes after stopping the injection. At the autopsy we found the blood of a blackish-brown color; nothing in the lungs; almost no urine in the bladder. The quantity of urea which had been introduced into the blood was about five hundred times greater than that which the blood contains in the natural state. We might ask if the accidents were due to the toxicity of this solution or to its degree of concentration, which might have modified the physical conditions of the blood-globules or of the cells of the tissues.

The experiments which I have just cited appear to disagree with the recent researches of Gréhant and Quinquaud. Death supervened, in their experiments, after injection of 6 grams of urea for each kilogram of animal; but the injection was made into the cellular tissue. Now, the additional loading of blood by urea could only have been produced if the whole dose had penetrated, all at once, into the circulation, which is scarcely possible by the subcutaneous method. These experiments, interesting from an experimental point of view, are without clinical application.

Six and thirty-one one-hundredths grams of urea are necessary to kill 1 kilogram of animal; *to kill a man* of 60 kilograms it would require, therefore, that his blood should retain more than 380 grams of it at one time. But 1 kilogram of man forming, in twenty-four hours, only 0.33 grams of urea, or 20 grams for each 60 kilograms, it would require, in order that his death should be due to retention of urea, that he should make nineteen times more of it ($\frac{380}{20} = 19$) in twenty-four hours, and that he should not eliminate any of it during that time; or that, making the normal quantity, he should remain nineteen days without eliminating any.

Some have incriminated uric acid as the cause of the toxicity of urine. But it is made in our body in far too minute a quantity (50 to 60 centigrams in twenty-four hours), and the gouty man can have hundreds of grams of urate in his deposits without being intoxicated by it. Besides, I have been able to inject experimentally into the blood 30 centigrams of uric acid for each kilogram of animal without apparent accident; I have even been able to inject as much as 64 centigrams of uric acid in solution in 160 cubic centimeters of water, to which the necessary additional quantity of soda had been added to produce its solution.

### EXPERIMENT BEARING UPON THE TOXICITY OF URIC ACID.

March 8, 1886. We took 1 gram of uric acid, which we dissolved in 1 cubic centimeter of soda-lye and distilled water. We obtained 250 cubic centimeters of liquid. We passed through it a current of $CO_2$ until it caused visible alterations. We redissolved with a trace of soda and filtered. A rabbit, 1560 grams. Injection into the auricular veins of 250 cubic centimeters. The animal received 1 gram of uric acid, or, per kilogram, 0.641; it received of the liquid 160.35 cubic centimeters. It did not die. Removed, it was only sick. Urine alkaline, muddy, containing blood. Heated, this urine became slightly clear. Albumin was precipitated. We filtered it hot. On cooling, it again became muddy, in a very notable manner, and gave an abundant precipitate of basic urates. We filtered. Into the limpid liquid we poured a little acetic acid. We had again an abundant precipitate of acid urates. The murexide reaction was very distinct. One hour and three quarters afterward very strong convulsions, which were repeated, until death, —two hours and twenty minutes after the commencement of the experiment. Autopsy: numerous foci of pulmonary apoplexy. Nothing in the other viscera.

The animal died slowly, and another experiment, performed for comparison, in which I injected the same quantity of water and soda without uric acid, has proved to me that death was alone due to the excess of the vehicle. *En résumé,* 1 kilogram of man forms, in twenty-four hours, 8 milligrams of uric acid. We are far from accounting for, by means of this agent, the intoxication which 10 to 20 cubic centimeters of urine produce.

### CONTROL EXPERIMENT MADE WITH THE SAME QUANTITY OF SODA-LYE WITHOUT URIC ACID.

March 10th. We made a solution of 1 cubic centimeter of the same soda-lye which had served for the previous experiment in a quantity of distilled water sufficient to make 250 cubic centimeters. We passed through it a current of $CO_2$ until it was neutralized, and we injected some of this into the veins of a rabbit weighing 1460 grams. It received 236 cubic centimeters of this solution, or 160 cubic centimeters of liquid per kilogram. The injection was made at 4 o'clock; it lasted fifteen minutes. At 7.30 the urine was bloody, limpid, acid. After coagulation of the albumin by heat, filtration, and cooling, no precipitate was produced; nor was there produced any greater precipitate, in this same filtered and cold liquid, when we added acetic acid to it. Died during the night. The only difference between this and the last experiment is that the first rabbit received uric acid, while the second received none at all. The results being the same in the two cases, it is clear that death ought to be attributed to this excessive quantity—viz: of water, 160 cubic centimeters—injected per kilogram of the animal, and we know that distilled water produces death after 122 cubic centimeters. Therefore, with 64 centigrams per kilogram, uric acid is not toxic. I add that we can never introduce into the veins of an animal more uric acid than in the first experiment, since this dose of uric acid would saturate a quantity of water which, of itself alone, is toxic.

We might also continue the demonstration for creatinin, but the experiments, already old, of Ranke and Schiffer having established that it is not toxic, enable us not to insist further upon it. Besides, we shall return, on another occasion, to this experimental investigation.

I have given some attention to the part which coloring and odoriferous substances may play in toxicity. Evaporation, which drives off odoriferous materials, increasing the toxicity of the urine, puts them sufficiently out of all causal influence.

Also, as regards the coloring principles, I have proceeded in the following manner: I estimate the toxic power of a urine by a natural injection. I decolor it by charcoal. I inject this decolored urine, and I ascertain that it has lost nearly one-third of its toxicity. A quantity equal to that which killed only produces accidents that are scarcely perceptible. It produces particularly nothing more than pupillary contraction.

### INTRAVENOUS INJECTION OF URINE, COLORED AND DECOLORED.

December 4, 1884. 1. We injected 65 cubic centimeters of a mixture of urine, taken from two healthy men, filtered and neutralized, into the auricular veins of a rabbit which weighed 1650 grams, or 39 grams for each kilogram.

We soon produced a pupillary contraction, very marked, but not pin-pointed. The animal, after the injection, was very much depressed. The temperature, previously 39.2° C (102.6° F.), fell to 38.4° C. (101.2° F.), and then to 37.8° C. (100° F.).

2. We injected 102 cubic centimeters of the same urine, after having decolored it, into a rabbit weighing 1670 grams, or 64 grams for each kilogram. The pupil was not contracted. The animal appeared, after the injection, much less indisposed than that in the previous experiment. Temperature before, 39.2° C. (102.6° F.); after it, 38.6° C. (101.5° F.).

We are, therefore, tempted to say that one of the toxic agents of urine is a substance removed by charcoal, and, as the coloring substances have this property, of attributing to them one-third of the toxicity of urine; but the conclusion does not follow, for, along with the coloring material, other substances may be fixed in the carbon.

One-sixteenth of the potass is arrested by the charcoal, and nearly the whole of the alkaloids. If decolored urine, which has lost one-sixteenth of its potass, has lost, at the same time, one-third of its toxicity, then it follows that in the urine there is something toxic besides the potass. And if the urine, which has lost the whole of its alkaloids, still retains two-thirds of its toxicity, then it follows that the toxicity does not wholly reside in the alkaloids. When we exhaust the dry residue of the urine by means of alcohol, we see that the alcoholic extract, which really contains the greater part of the alkaloids, is sensibly less toxic than the residue insoluble in alcohol, which ought to contain only a few of the alkaloids. Charcoal, therefore, removes from urine the substance which causes contraction of the pupil, but not all its toxic principles.

Let us follow the analysis of the toxic properties of urine by means of extracts and by adopting the dichotomic method. We shall evaporate a measured quantity of urine whose toxicity is known. The dry residue is washed, at different times, in absolute alcohol, and then we evaporate to dryness the whole of the alcoholic liquids. We thus, obtain two extracts,—the one containing substances soluble in alcohol, the other substances insoluble in alcohol. These two extracts having been dissolved in water, we have two solutions,—the one representing the substances of the urine which are soluble in alcohol, the other the substances which are insoluble in alcohol. We gauge the toxicity of these two extracts. We establish the fact that both are toxic, but in different ways.

### INJECTION INTO THE VEINS OF A RABBIT OF THE AQUEOUS EXTRACT OF NORMAL URINE INSOLUBLE IN ALCOHOL; DEATH.

November 11, 1884. We take 200 cubic centimeters out of the whole quantity of 1300 centimeters of normal urine passed in twenty-four hours. We evaporate to dryness upon the water bath with chloride of calcium; the residue has been washed in absolute alcohol; all the alcoholic liquids poured together, filtered, have been distilled in the retort to dryness; the residue is the extract soluble in alcohol. The residue of the washings in alcohol taken up by the water represents the substances of the urine insoluble in alcohol. This aqueous solution of the residue insoluble in alcohol occupies a volume of 48 cubic centimeters. It is introduced by intravenous injection into a rabbit weighing 1610 grams.

After the entrance of 12 cubic centimeters the animal is seized with tonic convulsions accompanied by straightening of the head. These convulsions rapidly disappear after we discontinue the injections.

At the end of 42 cubic centimeters the animal is seized with a violent tonic convulsion with opisthotonos, vibratory tremor, and it dies. At no period did it present contraction of the pupil except immediately after death. Temperature before injection, 39.2° C. (102.6° F.); at the moment of death, 38.6° C. (101.5° F.). Symptoms commenced on the entrance of 31 grams of urine for each kilogram, and death supervened when we had injected the insoluble extract from 108 grams of urine.

### INTRAVENOUS INJECTIONS OF THE ALCOHOLIC EXTRACT OF NORMAL URINE; DEATH.

November 11, 1884. Of 200 grams of urine treated in the same way as we have said in the previous experiment, we take the extract which is soluble in alcohol. This extract, containing 3.90 grams of urea, is diluted with distilled water in such a manner as to have a volume of 39 cubic centimeters. Urea is found there to be one-tenth. We inject 33 cubic centimeters of this solution into the veins of a rabbit which weighs 1870 grams. We see the pupil contract rapidly; after the tenth centimeter it is markedly contracted. Starting from this moment its diameter oscillates, but up to the end of the injection it remains smaller than in the normal state. From this point of view this result is exceptional; as a rule, the pupil is contracted more by the aqueous than by the alcoholic extract. The animal has no convulsion, but it falls gradually into a state of sleepiness; remains unmoved; lies upon its side; its pupil gradually dilates and becomes very large. During this comatose period the rabbit salivates and urinates abundantly. The initial temperature, which was 39.4° C. (102.9° F.), falls in a few minutes (ten or more) to 38.8° C. (101.8° F.).

In this experiment, the contraction of the pupil was manifested, under the influence of the soluble extract, from 27 grams of urine for each kilogram. The last symptoms corresponded to the injection of the soluble extract, from 90 cubic centimeters of urine for each kilogram.

November 12th. The animal died during the night. Nothing special at the autopsy.

The toxicity varies according to the individuals who have furnished the urines. The toxicity of each of the extracts is less than that of the whole urine. The manner in which they show their toxicity is different. Thus, the solution from the dry extract of substances soluble in alcohol produces somnolence, deep coma, diuresis. It does not cause a marked diminution of heat production (the small quantity of calorie lost is only equivalent to the equalization of the temperature, which takes place owing to the quantity of liquid necessary to inject the extract); it does not cause myosis, but a new symptom is caused, viz., salivation,—a salivation lasting three-quarters of an hour, and equal to that which is produced by jaborandi.

Here, then, is a fact, at first sight inexplicable. How can one part of the urine itself produce what the aggregate cannot? In order to salivate, it probably requires a measured quantity of the sialogenous material soluble in alcohol, and yet there exists an insufficient quantity of this sialogenous matter in the total quantity of urine to cause death.

Experimented upon in its turn alone, the extract of substances insoluble in alcohol produces myosis, like normal urine; also convulsions, which we never obtain with the extract of substances soluble in alcohol, but which we obtain exceptionally with the aggregate of urine. The convulsions are a phenomenon of later development; it requires a larger quantity of the extract insoluble in alcohol to induce convulsions than to bring about contraction of the pupil. We observe, too, in addition, diminution of temperature; but we neither obtain coma, diuresis, nor salivation. Thus, we are forced to admit that there is a plurality of toxic substances in urine. The tendency which we have to regard intoxication by means of urine as similar to that produced by certain alkaloids is not justified. Muscarine, for example, produces myosis and salivation, but we see these two phenomena dissociated when we experiment separately with the extract of substances soluble and with that of others insoluble in alcohol.

We can still say that coma, diuresis, and salivation are not produced by mineral substances, of which a very small quantity (some salts of potass) pass into the alcoholic washing; that the convulsions, myosis, and fall of temperature are not attributable to the mass of organic substances which have been caught in the washing with alcohol. Coma, which the soluble substances in alcohol produce, is never caused by urea. This causes, before death, no other phenomenon than diuresis; it does not cause diminution of temperature, and does not kill, except as we have seen it in enormous doses by preventing osmosis. That is what I mean. As for replying to other questions, as to the part which is played by such or such a body on the production of each of the symptoms observed after the injection of extracts, I cannot.

I do not know what is the substance which, passing with the urea in the alcoholic wash, produces coma.

Diuresis belongs to normal urine,—to the part of the extract soluble in alcohol,—as it does to urea, which, experimented upon in a purely isolated form, is certainly diuretic. I therefore think that it is urea which is the cause of the diuresis.

Urea does not increase salivation. Blood, which has a sialogenous power greater than urine, contains much less urea. I do not know what is the substance which produces salivation. I can only say that we find it in the blood, in the muscles, and in the liver.

What is it that produces myosis and convulsions? Is it the mineral substances? We are tempted to say that it is. Decolored urine, however, which has lost little of its mineral substance no longer causes convulsions nor myosis. Experimentally, after carbonization of the extract, the dissolved residue, which no longer contains anything but mineral substances, does not produce convulsions or myosis. Myosis is never produced; but if we inject more mineral material than the mass of urine contains which has killed without convulsions, we may induce death, and then it is always preceded by convulsions.

We might raise as an objection to this experiment that carbonization has caused to become volatile certain mineral salts, or that it has changed their chemical condition. But carbonization is not calcination; besides, in experimenting with fixed bases,—soda and potass,—we can appreciate the direct effects of these substances.

Soda is convulsion-producing. Neutralized by carbonic acid,—that is to say, under the form of bicarbonate of soda in dilute solution,—it induces hæmorrhages, by rendering the blood more fluid. As Magendie said, and as I established again experimentally in 1869, severe convulsions appear with a dose of 1.20 grams for each kilogram of animal, and death at 2.50 grams. But urine contains at the most 8 grams of salts of soda per liter,—that is to say, 48 centigrams for 60 cubic centimeters of urine. Urine contains, therefore, scarcely half of the soda capable of producing convulsions, and one-fourth of that capable of inducing death.

Potass is infinitely more toxic. Bicarbonate of potass causes death, with violent convulsions, in small doses of 5 centigrams for each kilogram of animal, and convulsions come on after a dose of 3 centigrams. Potass is forty-four times more toxic than soda; but if we find 2 grams of salts of potass per liter of urine,—that is, 12 centigrams for 60 cubic centimeters,—it is not in the form of potassium bicarbonate, but as chloride, sulphate, and other salts of potassium, which are less toxic, and whose degree of toxicity we shall investigate later on. We can, nevertheless, admit that for potass there is a limit as to toxicity. If there is an excess of it in the blood, however little, convulsions and death may be the consequence of it.

When we inject a solution of mineral substances, obtained not by carbonization, but by calcination, we sometimes observe this paradoxical result: in order to kill, it requires less of these substances than there is in the quantity of normal urine, the injection of which produces death. That explains, I think, how calcination has transformed into carbonates a part of the alkaline salts; and, as regards the same quantity of soda or of potass, the carbonates of these bases are two or three times stronger than the chlorides, sulphates, or phosphates.

Ammonia is toxic,—less than potass, but more than soda. At 15 centigrams per kilogram, ammonia, regarded as an anhydrous substance, and neutralized in water by means of carbonic acid, produces convulsions and then death. But normal urine only contains doubtful quantities of ammonia.

In short, of the mineral matters, potass is the one substance alone which, makes itself felt in the toxic totality.

I have finished telling you what I know of the part which belongs to each of these substances in the toxicity of urines which we suspect. I have said what I know, but not what we ought to know. Analysis and the isolation of various toxic principles from the urine ought certainly in the future to be carried further.

# LECTURE VI.

## TOXIC PRINCIPLES IN URINE—THE PART THEY PLAY IN PRODUCING URÆMIA.

**Recapitulation of the seven toxic substances found in normal urine. Diuretic substance, which is in reality urea. Useful function of urea. Narcotic substance. Sialogenous substance, whose action is not shown after the injection of normal urine, because it is found to be masked by more toxic substances. Two substances which cause convulsions. Organic convulsive substance, whose physiological action is habitually masked by its association with a narcotic substance. Substance which contracts the pupil. Heat-reducing substance, acting through diminished heat formation. Mineral convulsive material: potass. Neutralization of its action by a substance which produces narcosis. Analysis of the cause of death after double nephrectomy.——Comparison of the clinical symptoms of uræmia and of the physiological properties of the toxic substances of urine. Coma or convulsions: causes of the comatose form, convulsive or mixed. Dyspnœa. Myosis: importance of this sign, from a diagnostic point of view, as regards uræmia. Salivation. Hypothermia.——Diminution of the urinary secretion when urea ceases to be formed or is retained in the organism. Reinstatement of the urea. Additional toxic substances of urine, salts of soda, alkaloids. Heningham's criticism of urinary toxicity.**

AFTER having concluded the physiological analysis of the toxic principles of urine, if we recapitulate the substances which we have disassociated we find there are *seven* of them. There is, first, a *diuretic* substance,—fixed, of organic nature, since it is destroyed by heat. It is not fixed by charcoal; it is soluble in alcohol, and we find it mixed in the alcoholic extract along with other substances which have different properties. This substance possesses, besides the preceding characters, the property which experimentation allows us to attribute to urea,—that of augmenting the quantity of urine. We have thus the right to say that this diuretic substance contained in normal urine is no other than urea. Urea in this way, although it is a product of disassimilation, plays a useful rôle in the economy: it possesses the property of forcing the renal barrier; of removing, while making its own escape from the organism, both the water in which it is itself dissolved and other toxic matters which are united with it. Without doubt, urea is itself toxic. It is like every other substance,—like water itself, which, when introduced in sufficient quantity into the organism, can kill.

But in what dose is urea toxic? An enormous dose? It is necessary to fetter the functions of the organism; to introduce into the veins 5.5 grams to 6.3 grams of urea per kilogram of the weight of the animal. In the experiments in which we have killed rabbits by the injection of urea we required from 71.5 to 82 grams for 1000 grams of blood. There are, therefore, few bodies in the organism so feebly toxic as urea, if we except albumin and the water which naturally exists in the blood. Sugar is more toxic; we can, experimentally, scarcely introduce more than 5 grams per kilogram, or 65 grams per liter of blood. Yet, in order to kill immediately by intravenous injection of a sucrose liquid, we must introduce almost 10 grams per kilogram of the rabbit, or 130 grams per kilogram of blood. In pathological blood there may be 8 grams of sugar per kilogram of blood; but in pathological blood urea has been found in quantity at least equal. Among the mineral substances the most inoffensive, even bicarbonate of soda, which we so readily prescribe therapeutically, cannot be injected in a larger dose than 2.50 grams per kilogram of animal, 32 grams per kilogram of blood. In order to kill 1 kilogram of a rabbit 5 grams of chloride of sodium are sufficient; 6 grams of phosphate of soda; 9 grams of sulphate of soda. Urea has almost the toxicity of the most inoffensive salts.

We might say that urea, by inducing renal secretion, is eliminated quickly, and that this rapid elimination protects us against its toxic influence. The reply to this objection is found in nephrectomy followed by injection of urea: an experiment already performed by Bernard. In one of my experiments of the intravenous injection of urea in the rabbit, the animal was dead after the introduction of 6.31 grams of urea per kilogram. It had not urinated during the experiment, and at the autopsy the bladder was empty. Besides, however active the renal circulation may be, the rapidity with which the quantity of urea that we inject is found, as having entered into the circulation by our method of intravenous injection, is such that the elimination has not time to occur, and the physiological properties of urea show themselves immediately.

We have afterward met with in the urine a substance truly toxic. It is *narcotic;* it is fixed, of organic nature; is not fixed by charcoal; is soluble in alcohol, and is found in the alcoholic extract with urea and other substances. Certainly it is not urea, since in the experiments made with urea we do not see it produce narcosis. This narcotic substance which the urine contains I cannot name to you; a chemical analysis of it has not been made. We can only designate it by enumerating some of the physical, chemical, and physiological characters which we have found belonging to it.

A third substance is *sialogenous;* it produces salivation. Its presence in urine could not be suspected from the injection of normal urine; the total quantity of urine sufficient to kill does not contain this sialogenous substance in sufficient quantity in order to produce its physiological effect. We only see salivation appear after the injection of urine deprived of a part of its toxic substances; that is, of those which lead up to death too rapidly without giving time for the sialogenous substance to show its properties. This substance is stable, organic, not fixed by charcoal, soluble in alcohol like the preceding, but it is distinct from urea as well as from the narcotic substance. It certainly comes from the body like urea, for we find it in the blood, the liver, and the muscles in a greater quantity than in urine, but urea is only found in minimum quantity in the extracts of blood and muscle. We do not yet know its name or its chemical nature; we are only on the threshold of discoveries which yet remain to be made in the chemical analysis of urine; we have only succeeded so far in dividing urine into several parts, in each of which one day we shall isolate those bodies of which we are only able to suspect the presence.

We find in urine two substances endowed with the *property of causing convulsions:* one is fixed, stable, organic, since it is destroyed by carbonization, but retained by charcoal; it is, therefore, not mineral; it is insoluble in alcohol; it might belong to the group of coloring substances, from the manner in which it behaves; it is really an alkaloid, since it is insoluble in alcohol either in the form of a salt or a base. This organic matter which determines convulsions is found in less quantity in the urine of the day period than is the narcotic material, but it is of less physiological activity; and if injections of normal urine do not often produce convulsions, it is probably because the narcotic substance kills the animal before the convulsive substance has had time to exhibit its properties. In order to produce convulsions it is necessary to remove first from the urine the poison which kills rapidly. Of this convulsive substance we also do not know the name. Then there is a substance which causes *contraction of the pupil;* fixed, organic, attaching itself to charcoal; nonmineral; consequently it is comparable in certain respects with the substance which induces convulsions. We might suppose that it is mixed with it; that is to say, that one substance might be endowed with the two properties; we might also ask if it is not a coloring substance or an alkaloid. A coloring substance? It is possible. Alkaloid? Probably not, for the same reason that we have given when speaking of the convulsive substance. It is not probable that it is mixed with the preceding, for all normal urines contract the pupil, but it is very few of them which induce convulsions. It would be necessary to admit that the substance which convulses the sphincter iridis is more energetic than that which brings on general convulsions.

Urine produces pupillary contraction in small doses, from 10 cubic centimeters, and in general it causes death without convulsion in doses of from 30 to 50 cubic centimeters. We ought, with convulsive urines, at 60 cubic centimeters to see immediately happen contraction of the iris, while the phenomenon shows itself slowly enough. The separation of these two physiological effects shows that they belong to two different substances. We cannot give, any more than for other toxic substances, the name of that which causes contraction of the pupil.

We have met with in the urine a substance which *reduces heat.* It lowers the temperature by diminishing heat production, and not only like every cold liquid, which, introduced into the organism, subtracts from it a certain number of calories in order to put it into equilibrium with its own temperature, for when we inject a cold liquid into the circulation, we only produce a very slight fall of the temperature of the body; in reality, in this case, we stimulate calorification exactly as is done by the external application of cold: the organism tends to remake, by an acceleration of internal combustions, the calories which we have removed from it, and it restores really a part of it. After the injections of urine, on the contrary, the animal is colder,—not only as after every injection of cold water, because the organism puts itself into an equilibrium of temperature with the liquid injected, but because the organism loses a part of its heat-producing power. Each unit of weight of the body forms in a given time fewer calories than in the normal state.

The heat-lowering substance is fixed, organic. Ammonia also possesses the property of reducing temperature; but that of which we speak fixes itself on charcoal and is not, therefore, a mineral. It is insoluble in alcohol, like the preceding. It may be a color substance; it is certainly not the same material as that which produces convulsions, for we do not observe any proportion between the hypothermic effect and the convulsive,—no more than between these and the pupillary contraction. It is, therefore, a substance with an individuality of its own.

In short, we find in urine *another convulsive substance,* fixed, inorganic. It is, briefly, potass, whose toxic and convulsive properties we have known for a long time. Nevertheless, we cannot attribute to it alone the convulsions which the injections of urine produce, for, in order to inject potass in a toxic dose, very much larger quantities of urine would require to be injected. If we could get rid of, by means of charcoal, a convulsive substance which kills too rapidly, we might see convulsions come on and due to potass. If, in dealing with the extract which at one and the same time contains both the convulsive organic substance and potass, we destroy, by means of heat, the organic matter, convulsions are still produced, but there must be, occasionally, a double quantity of urine. Alcohol, it is true, has removed a part of the potass; sometimes however, in order to kill in convulsions, it is sufficient to inject the mineral substances taken from a quantity of urine less than the normal quantity of urine which produces death without convulsions. This paradoxical result, which I have already mentioned and attempted the interpretation of in the last lecture, might also be explained by the antagonistic action of certain organic substances which correct the convulsive action of potass.

*En résumé, there are two substances in urine which induce convulsions,*—one, *organic,* producing a rapid effect, which kills before the convulsions caused by potass could have been produced; the other, *potass,* a salt of which, viz., chloride of potassium, is convulsive and toxic at 18 centigrams for every kilogram of the animal. This neutralization of one toxic substance through admixture with another is seen under many circumstances. Atropine can neutralize the physiological action of pilocarpine. In the injections of normal urine the convulsive properties of the salts of potass are neutralized by their mixture with a substance which produces narcosis and coma. Thus, urines contain the antidotes to certain of their own poisons.

When we destroy the extract of urine by heat, the convulsive action of the residue is, perhaps, weakened by the volatilization of a part of the potass. In every case there is good cause for taking into account potass in the toxic phenomena consequent upon the retention of substances which ought to be eliminated by the urine; for the accumulation of potass may go on more rapidly than that of other substances coming from the organism. If, in consequence of failure in the elimination of the substance in urine which reduces calorification, disassimilation of the tissues diminishes, the potass which continues to be introduced into the organism by the food and drink may be soon found to be in a predominating proportion, and may induce convulsions, which is one of its properties. Thus, with urea, the urine contains seven toxic substances. To be exact, it would be necessary to say that everything in the urine is toxic, —everything contained therein, even water and soda,—but I say seven, including therein only the substances which are toxic in doses in which normal urine is experimentally toxic. This analysis, long as it may seem, of the toxicity of urines, is only an outline, which chemistry, without doubt, will complete, by the aid of improved methods.

It is sufficient for us, for the moment, to have demonstrated experimentally that urine removes poisons from the body; that the kidney plays a useful rôle; that it is a good emunctory;

that its suppression would be fatally hurtful to the economy,—an old opinion, which is sanctioned by the name of emunctory. Is it the case, however, that suppression of the urinary secretion is fatally dangerous? At first, proof appears to arise from the fact that death invariably follows double nephrectomy. We say that death is, then (in such), the result of an auto-intoxication. But the argument is not indisputable. There are many other modes of death besides nephrectomy. Might it not be that death was afterward caused by the want of elimination of water, or that the reflex paths of the renal plexus, being irritated, produce, in consequence of changes in the elaboration of the matter of the body, transformation of certain organic compounds, like that of urea, into carbonate of ammonia, or that new compounds were formed by reaction, and in an indirect manner? To this, as an objection, it has been replied that after nephrectomy we neither see produced anasarca nor œdema of the brain; that we do not find in the organism more carbonate of ammonia; that the reflexes could not of themselves have done so, since we have suppressed, in certain experiments, the track along which they have passed. Whatever the worth of this argument may be, in order to clear away the last point which separates us from certainty, it is necessary that we should find again in the symptoms of uræmia the physiological characters proper to the toxic matters of the urine. Does the clinical picture of uræmia supply this want? Œdema may be present, but it is rare.

We observe coma and convulsions,—sometimes one, sometimes the other of these symptoms,—probably because the kidney does not offer the same resistance to all the substances which pass through it. In interstitial and in parenchymatous nephritis it does not always retain the same materials,—salts, extractives, etc.; from these differences in its permeability for such and such a toxic substance might well result the predominance of comatose or of convulsive uræmia, or one of a mixed nature.

Dyspnœa is present in uræmia, with diminution of the range of respiratory movements. I may point to myosis as one of the constant characters of uræmia. In the evolution of choleraic phenomena we see in succession the intoxication proper to cholera and uræmic intoxication. When this latter arises myosis appears. All those suffering from the anuria of cholera have the pupil contracted. Myosis has already been pointed out by Roberts as one of the signs of anuria.

Salivation has been observed by A. Robin in uræmia. A subnormal temperature has been regarded as one of the commonest manifestations. What is wanting in the picture of uræmia so that it may be identical with that which poisoning by means of the toxic principles of urine produces? There is only wanting the abundance of the secretion induced by the great elimination of urea, for it is urea which is diuretic. Urea upon a diseased kidney can no longer exercise a beneficent influence. Besides, when urea is no longer formed in the body, the kidney—even when normal—ceases to show its functional activity. In hepatic uræmia, when the liver no longer forms urea, although the kidney remains normal, we often see the same symptoms arise as if it had become impermeable. We are thus led to this unexpected conclusion, that the substance urea, which has been for such a long time the scarecrow of physicians, is especially injurious when it is deficient. In the enumeration of the toxic substances of urine, I have neglected some, either because they are really scarcely toxic, like the salts of soda, or because they are only found in the urine in very small quantity. Such are the urinary alkaloids by which we have only recently tried to explain the toxic accidents of diseases in general, but which, although numerous in both the normal and pathological state, have not until now been proved, from our point of view of the toxicity of normal urine. They belong, without doubt, to the number of those indeterminate and unknown substances of which I have attempted to give a physiological analysis. M. Gabriel Pouchet said in 1880 that they were toxic: he saw them produce, in animals, muscular weakness, stupor, convulsions, then death, with the heart in diastole. But he had operated with the ethereal extract of large quantities of urine, and upon very small animals.

Confining ourselves to the limit of things applicable to pathology, if, instead of attending to the frog, we operate upon the rabbit, we find that the toxicity of these alkaloids is *nil* in the doses in which they are extracted from quantities of urine capable of bearing some comparison to man. The quantity of urine which would be capable of killing a man does not give off to the ether sufficient alkaloid to kill a rabbit.

I believe that I have not neglected, in this analysis of the toxicity of urines, anything but what was worthy of neglect. The alkaloids of the urine are interesting from the physiological point of view of their origin, but they do not seem to have the power of explaining by themselves alone the intoxication arising from normal urines.

[In the Journal of Pathology and Bacteriology, August, 1899, Dr. W. P. Herringham, of St. Bartholomew's Hospital, discusses at considerable length the methods employed by Bouchard and the deductions he has drawn from his experiments. Herringham does not consider that the injection of the *constituents* of urine separately into the blood-vessels of animals is a proper method, since this alters the relationship of the various substances of the urine that contribute to its toxicity. Feltz and Ritter in 1881 ("De l'uremie experimentale," Paris, 1881) showed that the urine of man and dogs was toxic, but that when the urinary constituents were individually injected they produced no serious symptom. After destroying by burning the organic constituents of urine they found that the injection of inorganic salts was much more toxic than the original fluid and they arrived at the same conclusion as Bouchard, viz.: that the principal toxic substances in urine are the salts of potassium.

Herringham has repeated many of Bouchard's experiments and after giving in detail the symptoms he observed he, too, is of opinion that potassium is the main poison. Bouchard's methods of experimentation are subjected to a lengthened criticism at the hands of Herringham, especially the manner in which this French physician reckons up the proportional toxicities of the inorganic substances in the urine. The absence of chemical analysis, too, it is maintained, weakens the value of his data, while no physiological support can be given to the opinion that the effect of small doses of any substance is similar to, but only weaker than that obtained when the same substance is administered in larger quantity. In confirmation of Herringham's contention allusion is made to the fact that atropine in small doses renders the pulse somewhat slow; larger quantities exceedingly rapid, while very large quantities again cause it to show similar conditions being observed in the administration of digitalis. Herringham, like previous experimenters, also found that potassium, reckoned as $KO_2$, was the main toxic body in urine, and that although the fatal dose of this substance lay between 0.1400 and 0.2100 gram per kilogram there were yet very wide variations; also that death came about not by cessation of respiration, but by heart failure. Of the salts of potassium it is the chloride that is the most toxic. Herringham states that the value of Bouchard's data is lessened by the fact that after incinerating the urine the residue was not analyzed, for the injection of the ash solution is found to be sometimes less, sometimes more, toxic than the original urine. Herringham observed, too, a new set of symptoms, a series of slow, irregular spasms like the athetoid spasms of hemiplegia, but upon what toxic agent these depend he cannot say. A number of experiments carried out by him went to prove that excess of pigment in the urine such as that caused by the addition of urochrome to it did not increase the urinary toxicity; also that there was nothing to show that the urine secreted during the day contained narcotizing material or that formed during the night contained convulsive substances, but that both properties were alike present in equal proportions in each urine. Herringham is distrustful of what he calls the mathematical accuracy of Bouchard's estimates of a "urotoxy" or the dose that is fatal to a kilogram; also of the "urotoxic coefficient," the amount of poison excreted by each kilogram *per diem*, urinary toxicity according to Herringham being nothing else than "an inexact expression of the excretion of potash." This is found to vary even with ordinary diet from 27.8 to 15. 2 urotoxies *per diem*, while in disease it may fall as low as 8 urotoxies, probably owing to loss of appetite being followed by diminished excretion of potash.]

# LECTURE VII.

## ORIGIN OF THE TOXIC SUBSTANCES OF URINE—TOXICITY OF THE BLOOD AND TISSUES.

The blood is unceasingly traversed by a current containing toxic material which, coming from the organs, is continually being eliminated by the emunctories; but blood ought never to contain at any time, in the normal state, more than an infinitesimal quantity of poison. Estimation of the toxicity of blood by experimentation and calculation. Toxicity of the liquor sanguinis. Comparative injections of blood into animals of the same and different species. Injections of blood-serum, of distilled water, and of artificial serum. Increase of the toxicity of blood by the destruction of globules, which disengage potass. Toxicity of aqueous and alcoholic extracts of blood.——Toxicity of the tissues and organs; difficulty of this research.——Toxicity of the extract of meat due to the presence of mineral salts, such as potass; and to organic substances, such as creatinin. Intravenous injections of extracts of muscle. Aqueous extracts of muscle produce convulsions, with the exception of myosis. The extract of muscle, deprived of the potass which it contains, does not produce any accident.——Toxicity of an extract of liver. Toxicity of bile. Various explanations offered. The toxicity of biliary salts is less than one would have believed; they probably act only indirectly in destroying anatomical elements and in setting at liberty mineral or organic products derived from cellular disintegration. Cholesterin possesses only an insignificant toxicity. The coloring matters ought to play a very important rôle in the toxicity of bile, since it, when once decolored, becomes much less toxic. Toxicity of bilirubin.

WE must now deal with the problem of the origin of the toxic substances which urine contains. Whence does urine obtain its toxicity? We have established the fact that the organism forms toxic products, and that the kidney eliminates them. It is now for us to show whether, on the side of the kidney, there is anything toxic in the blood and in the tissues. *A priori,* it is physiologically inadmissible that normal blood can be toxic. If it was, the animal could not live. We know that urine may be toxic—such as when found outside of the organism—in a reservoir from which it cannot be reabsorbed in the natural state; but blood itself cannot be, circulating, as it does, in vessels which are not opposed to its diffusion into the tissues. If blood is not toxic, it is because normal urine is, and is incessantly removing toxicity from it. The blood is continually being traversed by a current of toxic material. It is true that the poison is never found in it but in harmless quantities. There is less toxic matter in the blood than in the organs. The anatomical elements form substances which, if retained, would fetter their life; but these substances leave them, little by little, in order to penetrate into the blood. The quantity of toxic matter eliminated by the kidneys in twenty-four hours is, without doubt, one-half of what is necessary to kill the whole of the body, and the blood has really received that quantity in twenty-four hours; but the elimination is incessant, and at every instant of the day the blood never contains at one time more than an infinitely small fraction of poison.

The estimation of those fractions may be made for units of time; that is to say, for a complete revolution of the blood, say about forty-seven seconds, taking into account certain slower revolutions which take place in certain departments of the vascular system. A man of 65 kilograms expels in twenty-four hours 1350 cubic centimeters of urine, which kill 1 kilogram of rabbit with a dosage of 45 cubic centimeters. This man eliminates, therefore, in twenty-four hours, by his urine, sufficient to kill $\frac{1350}{45} = 30$ kilograms of living matter. The whole quantity of blood of this man is $\frac{65}{13} = 5$ kilograms. The 5 kilograms of blood of this man are thus traversed in twenty-four hours by a quantity of poison capable of killing 30 kilograms.

The number of complete circulatory revolutions is 1850 in twenty-four hours. In each complete revolution the kidneys remove from 5 kilograms of blood a quantity of poison capable of killing $\frac{30}{1850}$, and from 1 kilogram of blood $\frac{30}{1850 \times 5} =$ 0.003243 kilogram, or 3.243 grams. If, during a complete revolution, each kilogram of blood discharges a quantity of poison capable of destroying 3.243 grams of animal substance, in the same time this mass of poison will be furnished to each kilogram of blood by the organism, the ingoing being equal to the outgoing. It follows from this that the blood ought to contain constantly, at the least, this quantity of poison. It ought even to contain more, for the blood is, during each cardiac revolution, only deprived of a fraction of its quantity of poison by the renal emunctory. It is probable that there is in the blood more toxic material than this minimum portion which penetrates there, and which leaves it during the forty-seven seconds of a complete revolution, and that there is a reserve of toxic material circulating with the blood. Analogy helps to show us that it is thus as it ought to be, and it will enable us to appreciate hypothetically the importance of this reserve.

A man of 65 kilograms eliminates in twenty-four hours, by 1350 cubic centimeters of urine, 1300 grams of water and 24 grams of urea. In a complete circulatory revolution he eliminates 1850 times less of each substance,—that is, 0.7 grams of water and 0.01297 grams of urea. These quantities of water and of urea are given up by 5 kilograms of blood. One kilogram of blood gives, therefore, during one total revolution, five times less, or 0.14 gram of water and 0.002592 gram of urea. But this kilogram of blood only gives up these quantities of material from its liquid part,—from its plasma,—which constitutes one-half of the mass of blood; and the 500 grams of plasma in 1 kilogram of blood contain only 450 grams of water and 0.16 gram of urea. The calculation made, the blood loses, during a complete revolution, $\frac{1}{3214}$ part of water from its plasma and $\frac{1}{62}$ part of urea from its plasma, which proves, as I established in 1872, that urea is eliminated by the kidney fifty-two times quicker than the water ($\frac{3214}{62} = 52$).

If the rapidity of the elimination of the blood-poison was equal to that of urea, 1 kilogram of blood would contain sixty-two times the quantity of poison which this kilogram of blood eliminates in a complete revolution; and as this quantity eliminated is capable of killing 3.243 grams of living matter, 1 kilogram of blood ought to contain sufficient poison to kill $3.243 \times 62 = 201$ grams of living matter, which represents a minimum of toxicity.

If, on the contrary, the rapidity of the elimination of the poison was equal to that of the water, the quantity of toxic matter inclosed in 1 kilogram of blood ought to be 3214 times the quantity eliminated by this kilogram of blood during a complete revolution. One kilogram of blood would, therefore, be capable of killing $3.243 \times 3214 = 10{,}423$ grams of living tissue. This result is not preposterous; this maximum of toxicity would not be incompatible with life. With such a toxicity of its blood the animal would poison itself, if 1 kilogram of blood was distributed to 10 kilograms of its body; but, in reality, 1 kilogram of blood is distributed to 13 kilograms of the organism. It is, moreover, extremely probable that the real toxicity of the blood is less, and that it is comprised between these two extremes.

These hypothetical calculations only show us the extreme limits of the possible toxicity of the blood. We can, fortunately, approach the question from the experimental side. The injection of the blood of an animal into the veins of another animal can produce death without the death being attributable to embolism and without the augmentation of the mass of blood being incriminated. The injection of 25 cubic centimeters of blood per kilogram of animal is invariably fatal. What proves that death in such is the result of an intoxication is that the fatal dose varies according to the part of the vascular apparatus from which this blood has been withdrawn. If, instead of drawing it from the general venous system, we remove it from the portal vein, 14 cubic centimeters are sufficient to cause death, instead of 25,—this blood being charged with putrid and biliary poisons taken from the intestine, and not having them as yet removed from it by the liver. But a kilogram of animal contains $\frac{1000}{13} =$ 77 grams of blood. After the injection of 25 grams of blood, this kilogram would contain 102 grams, and then the animal dies. We may therefore say that 102 grams of blood are sufficient to kill 1 kilogram of animal. In other words, 1 kilogram of venous blood retains, in the normal state, sufficient poison to kill 9804 grams of living matter.

These conclusions would be strictly exact if the blood injected came from an animal of the same species as that into which we make the injection. But, in my experiments, it is the blood of the dog which has been injected into the rabbit. I have reasons for believing that the blood is more toxic for an animal of another species than for an animal of the same species. In experimental studies bearing upon transfusion, we have properly said that the blood of one species is poisonous to another, but we have not made the estimation of the degree of this toxicity, and we have always gone away from this point with a false view that the blood of an animal is not toxic for an animal of the same species. While the blood of the dog kills a rabbit at the dose of 25 cubic centimeters per kilogram, I have known the blood of the dog injected into another dog to the extent of 30 cubic centimeters only produces a fleeting indisposition, while in the rabbit, in order to cause death, it is necessary to inject 126 cubic centimeters of blood of rabbit. This amount is considerable. It is true that it was a question of the injection of arterial blood. Death supervened by convulsions, with moderate pupillary contraction. The urine contained only traces of albumin,—none of blood, none of hæmoglobin. There were no hæmorrhages into any organ, except from embolic foci,—numerous enough, but very small,—of pulmonary apoplexy, to which death could not be attributed, the respiratory rhythm not having been modified before the final convulsion, which was very short. In this experiment the animal died when each kilogram of its body was irrigated by $77 + 126 = 203$ grams of blood. From this we infer by calculation that 1 kilogram of rabbits' blood is capable of killing 4926 grams of rabbit,—in round numbers, 5 kilograms. And we still further draw the inference, if you wish to refer to calculations just recently made, that by the kidneys the poisons of the blood should be eliminated twice more quickly than the water, but twenty-six times slower than urea. This remark is not without some interest. It shows that if the kidney cannot be got to eliminate urea, it may succeed in expelling blood-poisons, and that, in the case of auto-intoxication, the withdrawal of large quantities of serum, or merely of water, might not be without some utility. One last conclusion to draw from the experiment is that, in order that death may be produced by auto-intoxication, it is sufficient that the amount of the poisons of the blood should become two and one-half times greater than the normal quantity.

I give you the different steps by which I have entered into this study of the toxicity of blood,—the hypothesis, calculation, and experiment. I have no difficulty in recognizing that more recent experiments have obliged me to admit that blood has a toxicity still less than that which seems should be inferred from the preceding experiment. In blood, the plasma alone may be toxic. The living cells retain within themselves the inert or hurtful substances of which they are composed. In order that these poisons may act, it is absolutely necessary that they should be in solution; it is necessary that they should dialyze from the blood into the tissues; it is necessary that they should be in the liquid part,—nonliving,—in the plasma. There has, therefore, been good cause for experimenting upon the toxicity of the blood-serum. I have extracted from ten rabbits, by arterial bleeding, 600 grams of blood. The clot, after having been in an icebox for twenty-four hours, has furnished to me 260 grams of a limpid serum, scarcely tinged. This serum has been filtered and then injected into the veins of a rabbit. The animal died, after having received 125 cubic centimeters of serum per kilogram. Death was preceded by a distinct, but not punctiform, contraction of the pupil,—by exorbitism, by dilatation of the superficial veins, and, in the last moments, by the loss of ocular reflexes, by convulsions, and by a frothy, sanguineous discharge from the nostrils. The lungs, voluminous but pale, were dotted with patches of pulmonary apoplexy. There were no hæmorrhages at any other point in the body. The urine contained neither blood nor albumin. The heart continued to beat for a long time after death.

The serum constitutes about one-half of the mass of blood. I have injected, in this experiment, the poison dissolved from 250 grams of blood. The animal had already in its vessels, before the injection, 77 grams of blood. When it died, its tissues had at their disposal, per kilogram of its weight, the poison of 327 grams of blood; from this I am obliged to conclude that 1 kilogram of blood is capable of killing about 3 kilograms of animal.

Was death, in this experiment, due to toxicity of the blood alone? I would not dare to say so. I am obliged to take some cognizance of the apoplectic patch in the lung and of the sanguinolent oozing from the nostrils, which suggest the idea of plethoric hæmorrhages, and which raise the question whether the enormous increase in the mass of blood has not been the cause of death. Remember, however, that the animal died, after having received into its veins 125 cubic centimeters of serum, like the animal in the preceding experiment, after having received 126 cubic centimeters of defibrinated blood. Remember, too, that distilled water causes death when we introduce into the vessels more than 122 cubic centimeters of it. From this comparison you will be able to conclude that blood is less toxic than pure water. It is only apparently so, and, at the same time, a misuse of language. Water is not toxic, properly speaking, and a liquid which kills in a larger dose than water may be toxic. Water does not kill by its chemical composition, by toxicity; nor does it kill any more by its mechanical action,—by plethora; it kills by its physical action, by swelling out the globules and dissolving out the hæmoglobin. If you wish to know to what point it is requisite to increase the mass of blood in order that death may follow, or what is the limit at which plethora becomes fatal, it is necessary, as I have done, to inject into the veins water, to which a salt very slightly toxic has been added, and in such proportion that in this solution the globules of the blood are not deformed,—a solution of sea-salt, 7 parts in 1000,—an artificial serum. Yet, with such a liquid, death comes in the rabbit only when we have injected for each kilogram 396 cubic centimeters of the solution, or when we have multiplied the mass of the blood six times. In such it is really with plethora that we have to deal; death is the result of a mechanical effect, for during life the veins are seen to be extremely distended, injection becomes difficult and laborious, and the piston of the syringe is constantly driven back by the excess of the intravenous tension. All the liquid injected remains in the circulatory apparatus, for the urinary secretion is not increased; we do not find liquid either in the stomach, intestines, or serous cavities, and there is no œdema in any part, but we detect a focus of pulmonary apoplexy. There has not been any physical action, for the blood-globules are neither deformed nor decolored; there has not been any chemical or toxic action, for we have only injected 2.772 grams of sodium chloride, and to kill a kilogram of rabbit we require 5.31 grams of this salt. If in order to kill by plethora we must increase the mass of blood six times,—I have not even tripled it in my injections of serum or of blood,—I add that in these experiments death cannot be explained by a physical action, as when there is a question of distilled water. I have introduced into the veins a liquid which is the natural medium of the globules, in which they neither become swollen nor retracted. I come therefore to my first conclusion,—death is apparently only explained by intoxication; but, notwithstanding, I maintain a reserve, for it is not poisoning which could have provoked pulmonary apoplexy; something must have been added to the intoxication.

To avoid this something, we would require to inject the poison of the serum in a state of greater concentration,—the removal of the water, the removal, too, of albuminoids, which, I suppose, cannot be the toxic substances, at least, when we inject blood from one animal into another of the same species. That is what I have done; I have coagulated the albumin and concentrated by freezing the liquid got by washing the coagulum. In order to produce death, I have been obliged to inject the extract from more than 400 grams of serum representing 800 grams of blood; yet it was simply the extract from the serum of horse injected into the rabbit. In this experiment, 1000 of blood would kill 1250 of living matter. Calculation has forced us to admit that a kilogram of blood would be capable of killing at least 201 grams, and at the maximum 10,423 grams of living matter—experimentation has narrowed these extreme limits. It shows us that a kilogram of blood could destroy at the least 1250 grams, and at the greatest 3000 grams of living matter. The true index, as yet undetermined, is between these two extremes. Besides the plasma, blood contains globules. Do these globules increase the toxicity of the blood? Experimentally, no; yet these globules contain toxic materials, and even in large quantity; but they are materials belonging to the constitution of the globules, and these are living. Blood is only a tissue of mobile cells, which have, like every cell, a framework. What enters into the composition of this framework is inoffensive for the cell so long as it is living; but each cell contains potass, which it keeps combined with other substances, mineral or organic. This potass cannot injure living cells except when liberated by the destruction of other cells; in these conditions potass passes into the liquids, and its toxicity may then be shown. If we destroy the globules by boiling or by charring and inject the aqueous solution of this into the blood of an animal, we bring about convulsions and death.

Alcohol removes water from the cells, extractive matters, fat, cholesterin, and the salts of potass. With the alcoholic extracts of blood we induce muscular weakness, convulsions, and very rapidly salivation, as I pointed out apropos of a toxic substance in urine. It is from the blood that the kidney gets this substance which causes salivation. With the alcoholic extract of blood narcosis is observed only under abnormal circumstances. I have seen it produced in one case with the blood of a uræmic patient who was not eliminating toxic substances, but with normal blood we do not induce narcosis. Into the alcoholic extracts of blood there pass nitrogenous bodies, both basic and neutral; I cannot say to which of them the physiological phenomena of which I speak are due. I consider that the living globules are harmless, but that they furnish toxic matter when they are destroyed. I can only incriminate the potass liberated by this destruction. I cannot always accuse the alkaloids found, in normal blood, by Gautier and myself, for they are found in a still smaller quantity than that which urines contain, and we have seen that they represent only a minimum part of the toxicity of urine.

*En résumé,* blood contains, as we know, a reserve quantity of poison; a small quantity of this poison is incessantly eliminated by the kidneys; it receives from the tissues an equal measure of it; it contains, therefore, in the normal state, always a certain quantity. If elimination is prevented and the supply of it continues, accumulation of toxic material produces intoxication. We know what the quantity of toxic matter is that is introduced into the blood and eliminated by the kidney in a circulatory revolution, and we also know what quantity of living matter might be killed by this amount of toxic material; we can, then, fix the time necessary for 1 kilogram of blood to kill 1 kilogram of animal. This period is two days and four hours; that is a theoretical average. In reality, the time necessary is longer, because in uræmia there are produced functional derangements of the intestinal tube which prevent it absorbing the poisons which it contains, were it only the potass of alimentary origin; moreover, the formation of the poisons of disassimilation is prevented by intoxication itself; vomiting, chill. The poisons only act when dissolved in the plasma; the cells are not toxic while they remain alive. The materials constituting these anatomical elements are retained therein by the force of tension which resides in every living cell; but in case of death or rapid disintegration of the cell, freedom is given to all the substances which were part of its constitution,—potass, creatin, leucin, and other nitrogenous substances. The proteid matters would themselves be incriminated if it is true that they can, by undergoing certain modifications, pass into the condition of soluble ferments; the experiments of Alex. Schmidt would tend to make this a supposition. In every case, in spite of the work of the school of Dorpat, I do not believe that the intoxication produced by blood can be attributed to dissolved hæmoglobin. The result of the sudden or rapid destruction of blood-corpuscles is the production of such phenomena as muscular debility, salivation, convulsions, and death, but never narcosis, unless when we operate with the blood of a person who is uræmic or is suffering from choleraic anuria. Of those effects, some are due to the mineral constituents; from the potass, notably the convulsive phenomena arise; of the organic substances there is one which is present in the alcoholic extract of blood and urine, liver and muscle, and to which salivation is attributed.

After having studied the toxicity of the blood, it would be desirable to get to know the toxicity of the tissues. But this is a still more delicate research; we cannot inject them as they are into animals; we can only inject their extracts, and these extracts, these products of the disintegration of tissues, are toxic. The toxicity of the extract of flesh has been known for a long time. This may be of some utility from an alimentary point of view; to a certainty it is toxic. If it does not poison, that is because it has been introduced only in small quantity into the organism, and that it is being constantly eliminated; besides, in every aliment there are toxic substances, and every aliment would become a poison if renal elimination was not the safeguard of the body. It is said that what is toxic in the extract of meat besides the mineral salts, potass, are organic substances, such as creatinin, which in meat is in the form of creatin. The stimulating effects after muscular depression are attributable to it.

With the aqueous extract of muscle, which contains mineral and organic substances, we produce neither salivation nor narcosis, but convulsions, and, exceptionally, contraction of the pupil. In these phenomena of intoxication there is no place for the action of alkaloids; the alcoholic extract of muscle causes salivation. An alcoholic extract of liver causes an excessive salivation; the extract from 117 grams of liver determines death in the rabbit. When we know the toxicity of an extract, if we suppress the potass which it contains, we deprive it of its power of producing convulsions. For this purpose it is sufficient to precipitate it in the state of tartrate of potass. After this operation the extract of 216 grams of muscle, which caused convulsions and death, produces no accident whatever. Besides potass, there exist in the extracts of the tissues such bodies as tyrosin, leucin, butyric and acetic acids; they play their part in those phenomena of intoxication, during life, comparable to those which supervene after the absorption of the poisons of putrefaction.

Here is a remark of Gautier: "By the side of aërobic life there is anaërobic life, thanks to which the cell is able to live for some time without oxygen. The anatomical elements are still engaged in the phenomena of oxidation, but at this time they are taking oxygen into the tissue itself. If we weigh the respired oxygen, that mixed with the fluids drunk and in combination with the food, and on the other side the oxygen fixed in the carbonic acid exhaled by the lungs, the skin, contained in the dejections and combined in the excreta, we find absolute equality on both sides. But the free oxygen has not been sufficient; the respired oxygen does not explain the surplus of water and carbonic acid; the oxidations, therefore, have been made with the oxygen of the combinations; one-third of life is supported by oxidation without free oxygen." Nutrition is thus, on one side at least, comparable to fermentation when air is excluded.

Let us return to the liver and to its particular emunctory function. Bile plays, without doubt, a part in digestion, but it is a constituent of the excreta, and it undergoes, in part, absorption. Does the part absorbed produce intoxication? Schiff has told us that we can find bile in the blood just come from the intestine, but not in the general circulation. He has admitted that the bile is seized again by the liver, then secreted anew, and again retaken without cessation. If this perpetual circle is true, the liver would, therefore, act as a protector to the general circulation, as regards bile and other poisons. That is possible, but not emphatically demonstrated. In every case the contrary is true in pathological conditions; bile may impregnate the blood and tissues. Even in the normal state, in the dog, bile passes into the whole of the circulation; in this animal jaundice is physiological.

To return to man, may bile itself cause in him intoxication? For a long time we have suspected the toxicity of bile. Deidier, in the last century, made intravenous injections of bile from those who died of the plague. In our own century, at different times, there have been undertaken experiments to clear up this question. Bouisson concluded that filtered bile is inoffensive; that, unfiltered, it kills. It can bring about, like all viscid liquids, — like pure glycerin, — pulmonary embolisms. Von Dusch, Frerichs, and Bamberger have injected large doses of it, and have only rarely induced death. Vulpian has injected up to 250 grams of it into a dog during several days,—96 grams in one day alone. He has omitted to mention the weight of the dog. Supposing it to weigh 10 kilograms, the toxicity of the bile would be 9 cubic centimeters per kilogram of the animal,—that is to say, five or six times stronger than that of urine. That is little when we think of the fatal consequences which are attributed to bile. I have established that the bile of oxen, mixed in twice its volume of water and injected into the veins of a rabbit, produces death in the dose of 4 to 6 cubic centimeters of pure bile for each kilogram of animal. I have recognized, besides, that bile decolored by carbon loses two-thirds of its toxicity.

Of the toxicity of bile, numerous explanations have been offered. The biliary salts have been declared toxic in almost infinitesimal quantities; they have been found in such small quantity in the blood of those who have died from severe jaundice and from poisoning by phosphorus. Injections of taurocholate and glycocholate of soda, made by von Dusch, Huppert, and Kuhne, have produced scarcely any effect whatever. And yet the results obtained by Leyden upon the dog and frog have little in agreement with each other. Concurrently with M. Tapret, I have determined that the biliary salts in an aqueous solution of 2 per cent. kill 1 kilogram of rabbit; the cholate of soda, in the dose of 54 centigrams; and choleate of soda, in the dose of 46 centigrams.

We might incriminate cholesterin, but we have only been able to induce cholesteræmia experimentally, by processes too defective to enable us to draw from them any conclusion. The absurd quantities of cholesterin which have been introduced into the blood have only been done through the medium of soap and water, or of potass, which would kill of themselves. At any rate, among old people, the atheromatous abscesses which we find widely open in the aorta contain sometimes several grams of cholesterin without there being any poisoning from them. The coloring substances ought to be suspected by us as toxic agents, since bile, once decolored, is much less toxic. Equally with M. Tapret, I have shown that bilirubin kills in the dose of 5 centigrams per kilogram.

As for the biliary salts, they do not kill by direct intoxication alone. We can see under the microscope the harm which they do. They dissolve and break up the blood-globules, and also other cells,—striated muscular fibers and the cells of the liver. They therefore cause anatomical lesions, and intoxication arises from the setting free of toxic substances which enter into the composition of the cellular elements. This intoxication develops but slowly.

People intoxicated by bile are, therefore, in the condition of animals into whom we have injected aqueous or alcoholic extracts of the tissues. Among patients, so long as there is functional activity of the kidney, all goes on well; but if not, then they die intoxicated by the potass and by other products of cellular destruction. But it is not a primary intoxication; it is secondary, and is caused by the mineral or organic products, and from the breaking up of the anatomical elements.

Among jaundiced people, we indeed observe a rapid diminution of the weight of the body. In acute yellow atrophy of the liver, it seems that the muscles diminish in size. Besides, if the kidney functionates well in jaundiced people, their urine is very toxic, but not in the same manner as normal urine. This does not determine convulsions; jaundiced urine is convulsive, and not narcotic. In small doses, even absolutely decolored, it remains toxic; but it does not owe this property to the convulsive material of normal urine, since this remains fixed in the charcoal. The convulsive property comes to it probably from the potass, for bile produces nothing similar to it. Thus, jaundiced urines owe their toxicity chiefly to the waste products of cellular disintegration, and especially to the mineral products. We are now beginning to foresee what intoxication may be in the economy.

# LECTURE VIII.

## ORIGIN OF THE TOXIC SUBSTANCES OF URINE—TOXICITY OF THE FLUIDS AND OF THE CONTENTS OF THE INTESTINE (BILE AND THE PRODUCTS OF PUTREFACTION).

**Toxicity of the fluids. It is due to the disassimilation or destruction of cells. ——Products of disassimilation turned into the intestine by the liver. Toxic power of bile compared with that of urine. Dangers of absorption or retention of bile. How the organism protects itself against the toxicity of bile. Precipitation of a part of the biliary elements in the intestine and metamorphoses having for their object the insolubility of other elements; toxicity of jaundiced urines; diminution of the toxic power of jaundiced urine brought about by decoloring.——Putrefaction in the intestine caused by microbes which are found normally therein. Rôle of the hydrochloric acid of the gastric juice which neutralizes the activity of these microbes.——Are putrid substances toxic? Opinion of Haller. Experiments of Gaspard, Panum, Bergmann, Billroth. Koch's argument.**

IF animal juices are scarcely toxic, although they contain more poison than the quantity given up to the emunctories, the cells inclose poisonous substances which they retain because these substances are part of their constitution, and which, freed by the death of the cells, cause the fluids to become toxic.

These toxic substances are organized and mineral. Potass occupies the first rank among them; in the normal state it is a constituent of the anatomical elements, but not of the fluids. In the economy of the living animal a measured quantity of toxic substance exists in a state of combination in the cellular elements, and it is only by an abnormal modification of these elements that we see their poisons come into the fluids. The fluids contain notably only the exact quantity of potass which they carry to the tissues or to the emunctories; the potass, therefore, is only on its transit in these fluids.

The mineral and organic poisons are, therefore, in general, poisons of disassimilation; but in the organs whose disassimilation produces poisons there are those which liberate a part of the material of which they are composed immediately into particular canals, which conduct it to the exterior; *e.g.*, the glands of the skin, the liver.

Bile escapes direct absorption by the blood, but not all contact with it, since at the surface of the intestine it is in contact with the mesenteric capillaries; only the liver is still there to seize it anew and to throw it out again into the intestine.

Would bile be dangerous to the blood? Assuredly; its toxicity is less than is believed, but it is still considerable.

In an experiment of Vulpian we see that 10 grams of bile per kilogram of animal constitute a poisonous dose. We even see it kill with 4, 5, or 6 grams one kilogram of animal. Bile is therefore, at least five times (occasionally ten times) more toxic than urine. The small size of the gall-bladder and the small quantity of bile which we find in it postmortem would lead us to believe that this secretion is of little importance. We change that opinion when we know the quantity of bile secreted in twenty-four hours. According to Beaunis, we may value at about 1 kilogram the quantity of bile produced in twenty-four hours in man. From observation in cases of biliary fistulæ, Ranke found a mean of 14 grams of bile per kilogram of living weight for twenty-four hours. Von Wittich has obtained from such in a woman, in twenty-four hours, 528 cubic centimeters; and in a woman equally suffering from fistula of the gall-bladder, with complete obliteration of the gall-duct, I have seen the daily quantity of the bile reach 800 grams. Thus, if, in equal time, the urine eliminates half of that which would kill a man, bile eliminates thrice the quantity. The total quantity of bile is six times more toxic than the totality of urine.

### COMPARISON BETWEEN THE TOXICITY OF BILE AND THAT OF URINE.

A man of from 65 to 70 kilograms eliminates in twenty-four hours 1350 cubic centimeters of urine on an average, or about 20 grams of urine per kilogram. This urine can kill an animal of 1 kilogram after a dose of 45 cubic centimeters. Man, for each kilogram of his body-weight, eliminates, therefore, in twenty-four hours, by his urine, sufficient to kill $\frac{1000\times20}{45} = 444$ grams of living matter. A man of 37 kilograms eliminates in twenty-four hours 652 cubic centimeters of bile; that is, 13.45 cubic centimeters per kilogram. This bile can kill an animal of 1 kilogram at the dose of 5 cubic centimeters. Man, for each kilogram of his body-weight, eliminates, therefore, in twenty-four hours, by bile, sufficient to kill $\frac{1000 \times 5}{13.45} = 2690$ grams of living matter. From what precedes we may conclude (1) that 1 kilogram of living matter being killed by 5 cubic centimeters of bile and by 45 cubic centimeters of urine, *bile is nine times more toxic than urine;* (2) that, the quantity of bile secreted in twenty-four hours by 1 kilogram of man being capable of killing 2690 grams of living matter, while the quantity of urine secreted by 1 kilogram of man in twenty-four hours is capable of killing only 444 grams of living matter, *the toxic activity of the hepatic secretion is six times greater than the toxic activity of the renal secretion:* $\frac{2690}{444} = 6$. If all the bile which the liver secretes passed directly into the blood, man would be poisoned by his own bile in eight hours and fifty-five minutes. If all the urine that the kidneys secreted passed directly into the blood, man would be poisoned by his own urine in two days, six hours, and thirty-two minutes.

We see the danger which results either from any impediment placed in the way of the elimination of bile or from its absorption. Fortunately, more than one-half is eliminated in twenty-four hours by the digestive canal; the water of the fæces represents the water of 400 grams of bile. Besides, the other half of the bile is not absorbed, for if it was eliminated by the urine the toxicity of urine would be much more considerable. We would be obliged to admit that the urine of twenty-four hours was capable of killing the whole individual, or even twice the individual; but experiment has shown us that urine has not this toxicity.

What becomes, then, of this half of the bile which is not thrown out by the digestive canal? Does the liver destroy it? Do the tissues change it? These two hypotheses are possible, but not demonstrated.

What is demonstrated is that in the intestine a portion of the bile ceases to be absorbable. The coloring matter and the biliary salts are metamorphosed,—precipitated or rendered insoluble. Yet, in certain morbid conditions, bile may be absorbed in the liver itself, at the margin of the hepatic cells. In these cases, if the kidneys remain permeable, it becomes a menace to intoxication; if they have ceased to be so, poisoning is the result. If the kidney has remained permeable, and no general accidents have arisen, the urine becomes toxic,—not to the individual himself, but to the animals upon which we experiment. Certain jaundiced urines are toxic at the rate of 13 cubic centimeters per kilogram; these urines owe, without doubt, a great part of their toxicity to the presence of coloring matters, since, once decolored, they may be injected in double or triple the quantity; but the destruction of the blood-globules and hepatic cells, the products of increased disassimilation, which the rapid diminution in weight among jaundiced people bears witness to, and especially the potass, contribute to rendering jaundiced urines very toxic.

### INTRAVENOUS INJECTION OF A HIGHLY JAUNDICED URINE.

March 11, 1885. Into a rabbit weighing 1650 grams we injected 22 cubic centimeters of a very pronounced jaundiced urine, coming from a patient in the Saint Landry Ward (Hôpital Lariboisière), who was passing 900 grams of it in twenty-four hours. After the sixth cubic centimeter, agitation. At the ninth cubic centimeter, pupil in great part contracted. At the fifteenth cubic centimeter, pupil pin-point; spasms; hurried respiration. At the twentieth cubic centimeter, screams; spasms. At the twenty-second cubic centimeter, death,—the heart still beating. The animal received *13 cubic centimeters per kilogram.*

### INJECTION OF THE SAME URINE DECOLORED, IN NEARLY TRIPLE QUANTITY.

We completely decolored, by means of animal charcoal, a portion of the urine which served for the preceding experiment. We injected into the veins of the ear of a rabbit weighing 1680 grams 50 cubic centimeters of this urine. The injection was driven in pretty rapidly. At the twenty-seventh cubic centimeter, slight tonic shaking,—stronger at the forty-first cubic centimeter. At the forty-eighth cubic centimeter, spasms,—not ceasing even at the fiftieth cubic centimeter. At this moment tonic convulsions, with opisthotonos. Respiration, which had become rapid after the twenty-fifth cubic centimeter, stopped; but the animal returned to life. At no moment had the pupil been contracted. The rabbit had received *30 cubic centimeters per kilogram.* On the 12th of March the rabbit had diarrhœa and much albumin in its urine. On the 14th of March it was quite well.

### INTRAVENOUS INJECTION OF JAUNDICED URINE.

March 14, 1885. Forty-five cubic centimeters of urine from the same patient whose urine had served for the preceding experiments were injected into a rabbit weighing 1450 grams. Spasms commenced after 12 cubic centimeters. At 20 cubic centimeters the pupil began to contract. At 42 cubic centimeters it was punctiform. Spasms began and death came after 45 cubic centimeters, *or 31 cubic centimeters per kilogram.*

### INJECTION OF NEARLY DOUBLE QUANTITY OF SAME DECOLORED URINE.

Into a rabbit weighing 1300 grams we injected 70 cubic centimeters of the preceding urine, decolored by means of charcoal. Spasm came on after 68 cubic centimeters. The pupil was not contracted. Death came after the seventieth cubic centimeter. *That was 54 cubic centimeters per kilogram.*

If bile is toxic directly and indirectly, the intestine is already, so far as bile is concerned, a source of intoxication, feeble it may be, but still really so. From it there pass onward into the blood, in addition, other materials which are eliminated by the urine,—mineral salts (*e.g.*, potass) introduced by the food, and other toxic substances of alimentary origin. Nevertheless this is only a minimum portion of the poisons which the blood may derive from the intestinal canal.

There is a third source of intoxication for the blood; it is putrefaction: not only that which arises from the imperfect metamorphosis of digested matter, but that which the presence of micro-organisms in the intestinal tube incessantly maintains. In the digestive canal the conditions most favorable for the elaboration of poisons are realized. Therein are found nitrogenous substances, already peptonized; and peptones are, as you know, excellent culture-media for microbes. They are in association with a notable quantity of water in a tube at a constant temperature of 37 degrees. The digestive canal is constantly open exteriorly. Besides, the foods taken carry in with them putrefactive agents; respiration allows of the deposition of dust in the pharynx, which, with each movement of deglutition, is caught by the saliva, along with the micro-organisms which it conceals. The conditions favorable for the maintenance of putrefaction are so numerous that we ask whether digestion can ever go on normally. Fortunately, the organism secretes in the stomach, on the introduction of food, a juice which is opposed to fermentation. Experimentally, we know that 1.10 grams of anhydrous hydrochloric acid per liter prevents all fermentation; but the gastric juice contains more. We find therein, per liter, up to 3.30 grams, and even 5 grams, of hydrochloric acid, estimated as the fuming acid of commerce.

But infectious agents have not been destroyed by the gastric juice in the stomach; they have only been neutralized; they have only passed into a state of latent vitality. The action of organized ferments recommences when the foods have passed through the pylorus. The acid of the gastric juice finds itself at this moment neutralized by the alkalies of the intestine, whose contents, if not alkaline or neutral, are in every case only feebly acid by a commencement of acetic fermentation.

We have regarded the bile as capable of prolonging the arrest of fermentations; but bile is capable of undergoing fermentation itself, or putrefying. It can, therefore, only feebly oppose fermentation in the small intestine. At any rate, it can have no influence upon those which are actively carried on in the large intestine.

Thus do we find the small intestine, on the one hand, and the large intestine particularly, on the other, capable of passing products of putrefaction into the blood. But, are the putrid substances toxic? Haller believes they are not. Gaspard, in 1822, established the fact that putrid substances are toxic, and that they are actually more so than substances arising from disassimilation. He injected into the veins of animals liquid arising from putrefaction of blood or of meat. He induced faintness, diarrhœa, and vomitings; hyperæmia of mucous membranes; then death; and at the autopsy ecchymoses of the digestive canal were seen; also of the cellular tissues,—those of the muscles and of the heart; swelling of the spleen and the mesenteric glands; congestion of the lungs,—phenomena all of which were verified by those who have since repeated Gaspard's experiments.

Magendie has studied intoxication by gases from the basins of water-closets,—he had previous knowledge of the morbid influence of putrid emanations.

The experiments of Gaspard have been regarded as correct by Panum, Bergmann, and Billroth. It yet remains to be known whether the facts observed by Gaspard arose from intoxication or infection. So far as he is concerned, he could not distinguish putrefaction from infection, not having any knowledge of infectious agents. He injected into the blood of animals the products of the life of inferior organisms, and at the same time these organisms themselves. At one and the same time, therefore, he caused intoxication and infection.

Panum tried to solve this difficulty. By boiling at 100° C. he destroyed the organisms themselves before injecting the products of putrefaction, and he, too, observed the same phenomena.

Koch has, besides, furnished another argument. If it is a question of intoxication, the effects produced ought to be immediate and proportional to the quantity of putrid matter injected. If it is one of infection a period of incubation is necessary, and the quantity ought not to seriously influence the accidents which follow. Experiment, however, shows that in those cases the accidents happen immediately after the injection of the putrid material. If we inject small quantities of it, we have accidents less grave than from large quantities.

Thus, the absence of incubation and the proportional ratio of accidents to the quantity of poison decide the question of their nature; they are truly of the order of intoxications. It remains, now, to isolate the toxic substances produced by the lower organisms.

# LECTURE IX.

## ORIGIN OF THE TOXIC SUBSTANCE OF URINE—TOXICITY OF THE PRODUCTS OF PUTREFACTION AND OF THE FÆCES.

Toxicity of the products of putrefaction in general. The accidents which they determine belong to the order of intoxications. Attempt to isolate the various products of putrefaction.——Panum, Hemmer. The sepsine of Bergmann and Schmiedeberg. Multiplicity of the alkaloids of putrefaction.——Zulzer and Sonnenstein, Selmi, A. Gautier, Brouardel, and Boutmy.——Variability of the products of putrefaction, according to temperature. Diminution of the toxicity of putrid substances owing to filtration through charcoal.——Enumeration of the toxic substances which putrefaction causes *in vitro*,—acetic acid, butyric, valeric, sulphuric, ammonia, leucin, tyrosin, indol, skatol, cresol, phenol, hydrocarbons, etc.——All these bodies exist also in the putrefactions induced in the interior of the digestive canal. They contribute to rendering the fæces toxic.——Demonstration of the toxicity of fæces. Stich. My researches upon the alkaloids of fæces; their multiplicity and their chemical characters. Intravenous injections of the extracts of fæces. Aqueous and alcoholic extract. Extract of fæces deprived of their mineral substances.——*Résumé* of the sources of toxicity. Kukula's experiments on intestinal obstruction. Hoppe-Seyler and Herter.

IT is proved that putrefaction gives birth to poisons whose effects are revealed in the putrid fever of Gaspard. We have wondered if death, in the cases which he observed, was really the result of intoxication. It is not explained by embolism, for we find neither the clinical character nor the lesions of such. Was it, then, a question of infection? Putrefaction, including, as it does, infectious agents and their products, we introduced all at once when we make injections of putrid substances. The results obtained are capable of being attributed to infectious accidents just as much as to toxic phenomena. The disease may be explained by multiplication in the blood of micro-organisms acting in accordance with one of the five methods which are proper to them. To this objection the experiment of Panum replies, for he only injected putrid matter after having heated it to 100 degrees; and he, also, observed the same phenomena as Gaspard.

Hiller introduced into the blood filtered putrid matter no longer containing any formed corpuscle visible under the microscope; he observed the same phenomena. Besides, I have recalled to you the theoretical argument of Koch,—if it was a question of infection, a period of incubation would be necessary in order that pathogenic organisms might have time to multiply in the circulation. The microbes which are the most rapid in their development require twenty minutes in order that one of them can give birth to two others. Besides, one microbe alone being quite sufficient theoretically to bring about infectious disease, a most minute quantity is sufficient to produce the most severe accidents. We know that the physiological effects are, in these cases, proportional to the mass of toxic matter introduced into the organism.

The toxicity of the products of putrefaction, taken generally, being once established, we ought to try to isolate each one of them. Panum, in 1856, made the first attempt at isolation. He evaporated to dryness putrid matter; exhausted, by alcohol, the dry residue; evaporated, by boiling, the alcohol from the alcoholic solution, and had thus two extracts,—the alcoholic extract and the residue, insoluble in alcohol, which would be the aqueous extract. Redissolving in water the two extracts, he studied comparatively the effects which each one might produce upon the living organism. He established thus the fact that the alcoholic extract is very feebly toxic; it represented one-fifth of the total toxicity. The substances insoluble in alcohol represent, consequently, the four-fifths of that toxicity.

Ten years later Hemmer showed that putrid poison is insoluble in alcohol.

In 1868 Bergmann and Schmiedeberg made researches upon the chemical character of the substances which cause putrid material to be toxic. They obtained a crystallizable body, comparable chemically to vegetable alkaloids, combining with acids to form crystallizable salts, and producing the same physiological effects as the injection of putrid matter. They have, therefore, considered it proper to ascribe to this body a rôle in the production of toxic accidents. This *sepsine,* as they called it, has been incriminated, since then, by surgeons, as the cause of certain complications of wounds (pyæmia, etc.). But already the experimenters of whom I have spoken had recognized, by the side of this sepsine, other bodies having a different toxicity.

In 1869 Zulzer and Sonnenstein had signaled out the presence of alkaloids in the products of putrefaction, having chemical reactions comparable to those of atropine, having the property of dilating the pupil and of accelerating the heart,—alkaloids which also exist (as I showed in 1882) in the extracts of the urine of patients attacked with typhoid fever.

In 1871 Selmi again extensively resumed the study of the question of the very numerous alkaloids of putrefaction, as well as Gautier in 1872, Brouardel and Boutmy in 1880, devoting their time to the study of the alkaloids of the cadaver.

The result of all these researches is that numerous alkaloids, variously toxic, are developed in the course of the putrefaction of organized substances. A putrid mass, taken *en bloc*, has a very variable toxicity. Its toxicity increases more and more in proportion as putrefaction advances. After the first products of the transformation of organized matter are destroyed, the toxicity, which has been at length increasing in it, afterward diminishes, and becomes annihilated at the end of a certain time. Putrefaction by heat develops a more intense toxicity; by cold, it is not only slower, but modified also in its intensity, as the following experiment proves.

As certain toxic organic substances lose a part of their toxicity after having been filtered through charcoal, I have caused putrid substances to be filtered. These lose a large part of their toxicity by this means.

### INTRAVENOUS INJECTION OF AN AQUEOUS EXTRACT OF MUSCLE PUTREFIED IN THE COLD.

April 30, 1885. We macerated, *in the cold*, 500 grams of muscle in 500 grams of water for twenty-four hours. We pressed it; we obtained 502 cubic centimeters of a distinctly colored liquid, and filtered it. We injected into a rabbit weighing 1850 grams 50 cubic centimeters of this liquid, or 27 *cubic centimeters per kilogram*. We observed a medium myosis and great depression. The liquid was not sufficient to allow of a larger injection.

### INTRAVENOUS INJECTION OF AN AQUEOUS EXTRACT OF MUSCLE PUTREFIED BY HEAT.

May 5, 1885. 1. We macerated 1200 grams of muscle in 1200 grams of water, in a stove, for two days. The liquid, strongly colored red, was filtered. Into a rabbit weighing 1720 grams we injected 40 cubic centimeters of this liquid. Death supervened, with dyspnœa and convulsions, but with little myosis, after a dose of *23.25 cubic centimeters per kilogram.*

2. We decolored, by means of charcoal, a certain quantity of this same liquid. Into a rabbit of 1480 grams we injected 100 cubic centimeters. Death supervened, with slight convulsions and myosis. The animal received *67.56 cubic centimeters per kilogram.*

The pupillary contraction which the injection of normal urine causes is also produced by the injection of putrid material, even though it has been filtered through charcoal. The toxicity of these substances is, therefore, due to another substance than that which exists in normal urine, since this, filtered through charcoal, loses its power of causing contraction of the pupil.

These researches are still only on the surface, so to speak. We have, at length, seen putrid intoxication in its entirety; we have afterward studied certain isolated parts of it. The alkaloids have been studied with some care; but the toxicity of putrefactive products is due to other causes than alkaloids. There is yet another series of toxic substances which putrefaction causes.

The acids,—acetic, butyric, valeric, sulphuric,—ammonia and the ammonia compounds, leucin, leuceine, tyrosin, indol, skatol, cresol, phenol, and the hydrocarbons are all toxic. All may and do contribute, in their part, to the toxicity of putrid substances, taken *en bloc.*

All that has just been said of putrefaction *in vitro* is applicable to putrefaction in the digestive tract, for the digestive canal is a veritable putrefactive apparatus. Moisture, heat, and the germs coming from the atmosphere concur in producing putrefaction as soon as the hydrochloric acid or the bile has disappeared or become changed in its nature. The alimentary residues which have not been digested and the peptones not yet absorbed are transformed, without any alteration, into infectious agents. Theoretically, in the second and, particularly, in the third parts of the intestine, there ought to occur the same phenomena, and the same bodies should develop which chemistry has revealed in experimental putrefaction. In fact, we find in fæcal matter the alkaloids of putrefaction (as I have shown, in 1882). They may develop there even under the influence of a ferment which is not organized,—trypsin. Since 1881 Tanret has seen that ether and soda carry into the peptones some substances having the characters of alkaloids, and which, in spite of certain analogies in chemical reaction, differ already from peptones by their solubility in ether. In 1883 Brieger demonstrated that alkaloids are developed during the act of peptonization. Fæcal matter contains also excretine, whose presence and toxicity Marcet has drawn attention to. Strong as was the presumption in favor of the toxicity of fæcal substances, it was yet necessary to demonstrate it briefly.

In 1853 Stitch showed that fæcal matter is toxic, but not to the individual who has produced it; because this experimenter introduced into the intestine of one animal the fæcal matter of another. In reality, fæcal matter is toxic, in a general way, to living cells. If we seek for those elements to which the toxicity of fæcal matter is due, we have only the embarrassment of choice. I will insist upon the alkaloids whose existence I demonstrated in September, 1882. I made extracts by means of chloroform and by ether, after having rendered fæcal matter alkaline.

I arrived at this conclusion, that fæcal matter contains various alkaloidal substances, some soluble in ether and insoluble in chloroform, others insoluble in ether and soluble in chloroform. All have the characters of alkaloids, behaving like them under the iodo-iodurated reagent, double iodide of mercury and potassium, phosphomolybdate of soda, tungstate of soda, and tannin. I have isolated them in notable quantities, but insufficient to produce intoxication. I believe, therefore, that putrefaction plays a part in the toxicity of fæcal substances, but less than is supposed. I have practiced intravenous injection with the extracts of fæcal matter.

The aqueous extract is toxic. It produces depression and diarrhœa,—phenomena the precursors of death. But it is chiefly the alcoholic extract which is energetically toxic in small doses. I have seen the alcoholic extract from 17 grams of fæcal matter kill, having induced severe convulsions. Now, man forms, in twenty-four hours, 400 grams of fæcal matter. We can seek for that substance to whose presence is due this toxicity of the fæces. The extract of fæcal matter, when it is deprived of its mineral substances, salts of potass, and ammonia, when it has been reduced to dryness, taken up again with absolute alcohol, treated by an alcoholic solution of tartaric acid, filtered, neutralized by sodium carbonate, evaporated, taken up again by alcohol, dried anew, and taken up by water, only kills in doses infinitely larger. It is no longer the extract from 39 grams of fæcal matter that we must inject to induce toxic and fatal accidents, but the extract of 298 grams.

### INTRAVENOUS INJECTION OF EXTRACT OF FÆCAL MATTER AND OF THE SAME EXTRACT DEPRIVED OF MINERAL SUBSTANCES.

April 28th. We collected on April 23d 600 cubic centimeters of fæcal matter, which we exhausted with 1 liter of absolute alcohol. The alcohol was filtered and distilled. The residue was taken up by 225 cubic centimeters of absolute alcohol. We afterward divided the liquid into two parts,—one of 150 cubic centimeters, representing 400 grams of fæcal matter; the other, 75 cubic centimeters, representing 200 grams of fæcal matter. *(a)* The second part (200 grams) was distilled and taken up by water. After filtration we obtained 90 cubic centimeters of liquid, of which 1 cubic centimeter represented 2.22 grams of fæcal matter. Into a rabbit of 1850 grams we injected 33 cubic centimeters of this liquid. At this moment convulsions, death. That is, 17.8 cubic centimeters per kilogram, or the *extract of 39.5 grams of fæcal matter.* *(b)*The first part (400 grams) was distilled and taken up by absolute alcohol. We precipitated the potass and ammonia by tartaric acid. We also neutralized, after filtration by sodium bicarbonate, filtered, evaporated, and took up by absolute alcohol. Again we filtered, evaporated, and took up by distilled water, and then filtered. We obtained 35 cubic centimeters of liquid, of which 1 cubic centimeter represented 13.4 grams of fæcal matter. Into a rabbit of 1340 grams we injected, by an intravenous channel, 35 cubic centimeters. No phenomena were observable. The rabbit received 400 grams of fæcal matter, or the *extract of 298 grams of fæcal matter per kilogram.*

We may, therefore, consider the following as contributing to the toxicity of the fæces: on the one hand, potass and ammonia chiefly; on the other, something which is soluble in alcohol, and which is neither potass nor ammonia; then bile; and, last, the residues of putrefaction.

To sum up: the aqueous extract of putrid matter is very toxic, that of fæcal matter is slightly so; the alcoholic extract of putrid matter is not very toxic, that of fæcal matter is decidedly so.

[In the preceding paragraphs Bouchard shows that it is particularly the alcoholic extract of fæces that is energetically toxic. Physicians are familiar with the fact that in patients who are the subjects of intestinal obstruction there are shock and a series of symptoms over and above those which neither the vascular condition of the wall of the bowel nor the blocking of the alimentary canal adequately explains. The prostration and collapse, which are usually very great, are much more probably the result of absorption and therefore signs of auto-intoxication. With the view of determining, if possible, what the substances are that produce the symptoms in intestinal obstruction Kukula (Archiv für klin. Chirurgie, vol. lxiii, p. 773) undertook a series of experiments. Two classes of poisons are known to exist in the alimentary canal: 1. Those arising in small quantities during normal digestion: *e.g., (a)* such products of carbonic acid fermentation as acetic, lactic, and butyric acids; *(b)* those from the putrefaction of albumins as $NH_3$, $CO_2$, $H_2S$, leucin, phenol, etc. 2. Chemical substances formed in stagnant or fermenting fæcal matter, *e.g.,* pyridin, toxalbumins, or ptomaines. Of these latter, Kukula attaches most importance to such of the diamins as tetramethylene and pentamethylene diamins, ethylene diamins, cholin and neurin. By the term diamins we mean bodies "in which two amin ($NH_2$) groups are united to a diatomic alcohol radical of the olefine series of hydrocarbons." In health the peristaltic movements of the bowel are promoted by the products of the first group when they are present in small amount. Should these be in excess they cause gastro-enteritis, whereas sulphuretted hydrogen, ammonia, and phenol are really toxic. It is the products of the second group, however, that principally cause auto-intoxication. Kukula injected subcutaneously toxins obtained from filtrates of intestinal contents into 39 animals, in most of whom no reaction occurred. Of 9 of the animals in whom he produced artificial intestinal obstruction, only 1 died, and of 5 animals in whom he produced strangulated hernia, 1 only died. The intestinal contents of the animals operated upon were not specially toxic. In 12 dogs he attempted to produce artificially intestinal obstruction, and succeeded in 7. Of these, 4 died in a few days with well-marked symptoms of intestinal obstruction, the lesion being confirmed by postmortem examination. The other animals were killed before presenting any characteristic symptoms. In the urine of all the animals Kukula found phenol and indican; he noticed that these substances increased progressively in the urine until the day of death or in the dogs that recovered until the function of the intestine was restored. Taking the intestinal contents of the obstruction cases he found that these, whether they were injected pure or as filtrate, caused poisoning. Like Bouchard, Kukula observed that the substances abstracted from fæces by alcohol were powerfully toxic and were especially so when administered by intraperitoneal injection than subcutaneously. To pentamethylene diamin, sulphuretted hydrogen and methylmercaptan is attributed the principal rôle in causing symptoms: symptoms which in a general way recalled those that are observed in man in intestinal obstruction and which are probably due to absorption of septic matter through the intestinal wall whose epithelial lining must become altered in this grave affection. In intestinal auto-intoxication there is absorption probably of more than one substance, gaseous or solid in solution.]

If we class toxic products together, we place in the first line mineral substances,—chiefly potass,—alimentary products, or those furnished by disassimilation; in the second line the products of intestinal putrefaction, among which ammonia occupies an elevated position; in the third line the organic products of disassimilation, and therein is included a small quantity of bile, which may be reabsorbed by the intestinal mucous membrane.

Thus we recognize all the sources of the toxic materials of the economy,—the tissues, secreting organs, foods, putrefactions.

The toxic products coming from these four seats of origin, introduced into the blood, give to it that slight degree of toxicity which we have been able to estimate. The blood imposes this toxicity upon the products of secretion, and especially upon the renal emunctory. After having demonstrated that the urine is toxic, I showed that it cannot be otherwise. The blood is not, to any extent, habitually toxic, because urine is strongly so; if this were no longer toxic the blood would become toxic, since poisons are always being introduced into it, proceeding from disassimilation, from foods, the products of intestinal putrefaction, and the products of secretion.

We never observe accidents the outcome of intoxication with normal kidneys; if the kidneys are diseased the individual dies. To all cases of death arising from suppression of the renal function we apply the term uræmia. But what we already know enables us to foresee that a complexity of phenomena is hidden under this name.

[Bouchard's main contention in this chapter, while indicating the sources of certain intestinal toxins, is that it is through the eliminating powers of the emunctories that auto-intoxication is prevented. To this safeguard we might add the influence of chemical changes determined by processes of oxidation and deoxidation, hydration and dehydration, that are normally occurring within the organism. The oxidative processes that are constantly taking place at the normal temperature of the human body are not known much beyond the fact that the red blood-corpuscles are continually parting with oxygen to the various tissues. While oxidation is therefore a vital act depending upon a splitting in the oxygen molecules leading to a separation of two atoms of active oxygen, which possesses the characters of the nascent gas. Combustion processes occur, on the other hand, in the liver whereby the complex molecules derived from food products absorbed from the intestine are converted into substances of a simpler chemical composition and less harmful character. It was Hoppe-Seyler's opinion that the oxygen is in these processes set free by nascent hydrogen formed in the course of certain decompositions, while Herter suggests that the iron in nucleo-proteids may play a part in oxidation through ferric salts being reduced to ferrous, these again becoming ferric by the renewed absorption of oxygen; also that the presence of hydroxyl (OH) ions in the blood and lymph may contribute "either by taking the place of hydrogen atoms or by liberating nascent oxgen simultaneous with the formation of water" (Herter, "Lectures on Chemical Pathology," p. 22), or it may be that these hydroxyl ions act through the hydroxides dissolving the carbonic dioxide that is constantly being formed by cells. Were it not for the constancy of these oxidation processes the human body would be much more frequently menaced by auto-intoxication and the eliminating organs more surely taxed. Taking indol as an example of a putrefactive alkaloid formed in the intestine during digestion, this is known to possess poisonous properties. After absorption indol in its passage through the liver is primarily oxidized by the hepatic cells into indoxyl, which, subsequently combining with sulphuric acid, is converted into indoxyl sulphate of potassium: a body not only less toxic than indol, but one more easily thrown out by the kidneys. By means of the oxidative and deoxidative processes that are taking place in the organism not only is considerable help given to the eliminating organs, but poisonous substances are deprived to a large extent of their toxicity.

The word "ion" recently introduced into physical chemistry calls for some explanation. An "ion" may be either an atom or a group of atoms as seen in the following: Water is composed of $H_2O$ and its molecules are in constant movement; these molecular movements become more energetic as the temperature is raised. Because the molecules of which it is composed undergo, practically speaking, no dissociation into their constituent atoms pure water is not a conductor of electricity. When a substance like sugar is dissolved in water, the solution still remains incapable of conducting an electrical current; the sugar molecules do not undergo dissociation. "But if a substance like salt is dissolved in the water, the solution is then capable of conducting electrical currents, and the same is true for most acids, bases, and salts. These substances do undergo dissociation, and the simpler materials into which they are broken up in the water are called *ions*. Thus, if sodium chloride is dissolved in water a certain number of its molecules become dissociated into sodium ions, which are charged positively with electricity, and chlorine ions, which are charged negatively with electricity. Similarly a solution of hydrochloric acid in water contains free hydrogen ions and free chlorine ions. Sulphuric acid is decomposed into hydrogen ions and ions of $SO_4$." . . . "Ions liberated by the act of dissociation are charged with electricity, and when an electrical current is led into such a solution, it is conducted through the solution by the movement of the ions. Substances which exhibit the property of dissociation are known as electrolytes. The liquids of the body contain electrolytes in solution, and it is owed to this fact that they are able to conduct electrical currents." (Halliburton, "Essentials of Chemical Physiology," p. 200, 1901.)]

# LECTURE X.

## INTESTINAL ANTISEPSIS.

*Résumé* of the causes of the toxicity of the contents of the digestive canal. Potass and ammonia, bile, putrid substances.——Poisons absorbed in the intestine must traverse the blood, since they are found in the urine. Parallelism between the toxicity of urine and that of material contained in the intestine. We can diminish the toxicity of urine by inducing disinfection and antisepsis of the digestive canal.——Influence of charcoal taken in a sufficient quantity upon diminution of the toxicity of urine.——On intestinal antisepsis. Conditions which a medicament ought to fulfill when destined to bring about intestinal antisepsis.——Salicylate of bismuth, salts of mercury, iodoform, naphthalin. Their advantages and inconveniences. Method of administering naphthalin.——Charcoal fixes the coloring matter and the toxic products of bile. Naphthalin is opposed to intestinal fermentation.

THE organism contains poisons the origins of which we know, viz.: the destruction of cells, disassimilation, secretion, ingestion, and putrefaction.

The digestive canal contains three orders of these poisons: those which come from the ingesta, bile, and putrid material. Its contents, therefore, should be toxic. Experimentation has demonstrated that they are toxic from potass and ammonia, from bile and putrid material.

There are, therefore, poisons in one part of the organism from which absorption is continually taking place. Can this absorption produce intoxication? We cannot demonstrate experimentally that the poison enters the blood, but we can demonstrate that it leaves it. It is, therefore, necessary to see whether the toxicity of the urine is in keeping with the toxicity of the digestive tube, and as to whether their variations are parallel.

In 1882, while demonstrating the alkaloids found in normal fæcal matter, I considered those as the source of nearly all the alkaloids of the economy. I have been able in one instance to estimate their quantity as 15 milligrams per kilogram of fæcal matter. I noticed that each time these alkaloidal substances increase in the fæces they increase in the urine, although always smaller in quantity. I noticed, too, that the parallelism is preserved not only from a quantitative point of view, but also as regards their nature. Just as there has been a predominance, in the digestive canal, of alkaloids soluble in ether or those which are soluble in chloroform, so have I seen predominate, in like manner, one or the other in the urine.

I am less inclined, to-day, to add so much importance to these toxic products. We can arrive at the same opinion by taking toxic substances in their totality.

We may suppress a part of the toxic matter of urine by fixing that of the intestine by means of charcoal, which retains the coloring substances and the alkaloids. This is to induce not antisepsis, but disinfection of fæcal matter.

The extract of 200 grams of fæcal matter, in the case of patients by whom we have caused to be ingested the required quantity of charcoal, is inoffensive to those animals into which we have injected it, while we killed with the extract of 17 grams, of fæcal matter not disinfected, per kilogram. This intestinal disinfection by charcoal diminishes also the toxicity of urine by from one-half to two-thirds. If we wished to push the inquiry further, it would be necessary to produce antisepsis by preventing even the putrefaction which is produced in the intestinal canal.

It is a long time since we have produced antisepsis without knowing it, just in the same way as M. Jourdain[1] made prose. By giving calomel, or the black sulphide, we diminish, without knowing it, putrefaction. Many physicians have done so consciously, supposing that substances with a putrid odor would be offensive to the elements with which they are in contact.

We have employed chlorine internally, and pure iodine,—excellent antiseptic,—the sulphites, hyposulphites, phenic acid, creosote (Pécholier), and boric acid. We have obtained nothing by these means save, perhaps, with the sulphites (Semmola, Pauli) and the sulphide of carbon (Dujardin-Beaumetz).

A reproach which at the outset we can theoretically raise in regard to all of these substances, with the exception, perhaps, of the last one, is, that they are soluble and absorbable. In the long journey from the mouth to the intestine the antiseptic agent loses some of its power. One other inconvenience which might arise from absorption of the antiseptic agent is that, when introduced into the blood in a sufficiently large quantity, it might exercise therein a toxic influence.

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[1] This refers to "Le Bourgeois Gentilhomme" of Molière.

The conditions which a substance should fulfill when destined to bring about intestinal antisepsis are that it should not be absorbable, and yet should be capable of being given in doses efficaciously antiseptic without inducing by itself any toxic influence upon the organism. We must, therefore, use insoluble antiseptics.

Salicylate of bismuth and iodoform, extolled by Vulpian; naphthalin (Rossbach); calomel, which is changed into bichloride in the stomach and black sulphide in the intestine; black sulphide employed alone (Serres, Becquerel), these have each in their turn enjoyed considerable favor. A portion of these agents is always absorbed.

Thus, with salicylate of bismuth the fæcal matter is blackened owing to the sulphide of bismuth, and the urine contains salicylic acid.

With iodoform, which I have employed for a long time now, we find a little iodine in the urine, and the stools contain free iodoform.

When we administer naphthalin the stools contain it. This body, hitherto considered insoluble in water, is absorbed to the extent of some centigrams for every 5 grams we have given. The urine rapidly takes on a brownish-black coloration, different from that of carbolic acid, which is tinted black, and from creosote, which is of a greenish black.

Acetic acid, in small quantity, modifies the substance which results from the passage of naphthalin into the urine. Under its influence a rosy tint appears, which acetic acid does not produce in normal urine. We can estimate in the urine a body of a compound-sulphur character, resulting from the combination of naphthol and sulphur, a naphthosulphurous acid, which may be arranged as naphthosulphite of soda. This union can only have occurred by sulphur having been borrowed from the organism; that is to say, by destroying albumin or nitrogenous matter.

But this quantity of sulphur is insignificant, as I have been able to ascertain by the aid of M. Rosenstichl. From the whole of the urine passed by a woman who had taken for ten days 5 grams of naphthalin we were only able to remove 0.03 centigram of naphthosulphite of soda per liter.

For ten years I have made use of charcoal in large doses, and, thanks to it, have obtained a diminution of the toxicity of urine and of fæcal matter without preventing fermentation. Since then I have added iodoform to charcoal, which neutralizes putrid ferments, according to the formula: charcoal, 100 grams; iodoform, 1 gram.

Following Rossbach, I experimented with naphthalin to solve the question of the seat of the infectious agent in cholera; then in typhoid fever, gastric fullness, putrid diarrhœas; finally, in the healthy individual, without injury to the latter.

I give the formula: 5 grams of naphthalin, mixed with an equal quantity of sugar, made aromatic with 1 or 2 drops of bergamot, divided into 20 powders, 1 of which is to be taken every hour.

Fæcal matter at length loses its odor, unless it is simply masked by that of naphthalin. But a second and greater advantage is that fæcal matter loses, to a great extent, its toxicity, the putrefactions within the intestinal tube being completely suppressed.

In the case of a man the subject of gastric trouble, 35 to 40 cubic centimeters of urine induced death for every kilogram of animal. After disinfection of the fæces by naphthalin from 90 to 100 cubic centimeters of urine were harmless. This harmlessness of the urine lasted as long as the antisepsis of the digestive canal. When antisepsis was suppressed the urine became toxic again.

With charcoal I was less enlightened upon the cause of the inoffensiveness of the urine, since it fixed the coloring matter of the biliary secretion. By means of naphthalin I only suppress fermentation. We would also require to suppress the bile; but as, in the case of people in whom bile ceases to flow into the intestine, it passes into the blood, the problem cannot be solved. We would require to have an individual the subject of biliary fistula, and suppress in him alimentation. All causes of toxicity removed, whatever will remain of a toxic character in the organism would be attributable to the poisons of disassimilation. Here is research for the future.

To sum up: I have succeeded in demonstrating that not only are there poisons in the intestine, but that they are a constant menace of intoxication to the organism. After having explained the sources of toxic substances, I have shown their passage through the organism, their elimination by the urine, and the sewage wave laden with toxicity coming from other sources. If urine is not formed, there may result from this fact intoxication, which will often be of intestinal origin. That is why, in place of uræmia, I have proposed to call it stercoræmia or copræmia.

If I have written at such length upon physiological data, it is because these were indispensable before undertaking the analysis of pathological facts.

# LECTURE XI.

## PATHOGENESIS OF URÆMIA—DISTINCTION BETWEEN THE SYMPTOMS OF THE PRE-URÆMIC PERIOD OF NEPHRITIS AND THE SYMPTOMS OF INTOXICATION.

**The knowledge of the action of the toxic substances contained in the urine does not explain all the symptoms of nephritis. It only explains those of the period of intoxication, when the organism produces more poison in twenty-four hours than the kidneys can eliminate in the same time. A normal kidney can eliminate more toxic material than it does in an ordinary way. ——Examination of the various accidents which we observe in diseases of the kidney before the uræmic period,—albuminuria, cachexia from hypo-albuminosis. Dropsy. Vascular and cardiac troubles; their effect upon the digestive canal and the nutrition of the skin. Hæmorrhages. Eye troubles. Spurious serous phlegmasias. All accidents precipitated may come on when the urine is still normal as regards quantity and density.——When the renal impermeability has become excessive, the period of intoxication is announced by one or several of the seven poisons which normal urine contains, variously associated. There would, therefore, be not one, but several uræmias. Clinical investigation has, for some time past, established various symptomatic forms, and the five theories actually in existence, which are proposed in order to explain the pathogenesis of uræmia, contain, all of them, an element of truth.**

WE know the various groups of toxic substances which, in the normal state, enter into the blood and are eliminated by the kidney. By lesions of the kidney allowing of the accumulation of toxic products in the organism, it is apparent that we can now clearly interpret the accidents which are produced in people who are the subjects of disease of the kidney. We must not delude ourselves, however; the physiological knowledge which we have acquired only throws light upon some of the accidents which complicate diseases of the kidney.

Among the symptoms of nephritis, many do not belong to the domain of intoxication. Besides, every disturbance of the renal function is not capable of determining a sufficient accumulation of toxic substances in the economy, and for symptoms to show it. In order that intoxication may be invoked, it is not sufficient that the kidney should be diseased. It is necessary that its permeability should be diminished to a degree such that it can no longer eliminate, in twenty-four hours, the quantity of poison which the organism forms in twenty-four hours. Now, it is certain that the kidney can, in the normal state, eliminate infinitely more toxic material than it generally does. Let us consider what a normal kidney can do. Instead of the 1200 to 1500 grams of urine which it secretes ordinarily in twenty-four hours, a normal kidney can secrete as much as 25 liters of urine, and more. Instead of 20 to 30 grams, it can eliminate 120 grams of urea, and more, as in a large number of cases of diabetes insipidus. Instead of 55 centigrams of uric acid, which the kidney eliminates in the normal state, it can, in cirrhosis and in leukæmia, eliminate 8 grams of it, and more, in twenty-four hours. It can, in addition, eliminate other abnormal substances, up to 140 grams of sugar per liter. Add to this the fat existing in the form of granules, and not dissolved (chyluria). The kidney also eliminates substances which it ought to retain,—peptones and albumin.

It requires the kidney to be considerably diseased, for, owing to its permeability, it is sufficient alone to eliminate the poison formed by the organism, in proportion to its production. Below this rate there commences intoxication; but before this arises we see abnormal phenomena appear, and, first of all, albuminuria.

Albuminuria is the accident of bad repute in diseases of the kidney,—that to which we attach extreme importance, behind which we find œdema and all the rapidly developed or slowly evolved accidents of Bright's disease, and which we regard as causing exhaustion. Yet it is often a few centigrams—at the most, a few grams—of albumin which the patient eliminates each day. Such a slight spoliation is not capable of causing deterioration of the system. A woman who is nursing loses, without any injury, 40 to 50 grams of albumin or other proteid matter by the lacteal secretion, and yet her system is not weakened thereby. Her safeguard is the integrity of her appetite and digestion. She loses albuminoid matter under one form and recuperates it under another. But, in the same way as in the nurse, insufficient alimentation and vomiting may diminish the proteids; and if the renal disease is accompanied by fever or other phenomena which prevent nutrition and reparation, intense albuminuria becomes a cause of exhaustion, like abundant leucorrhœa, dysentery, suppurations, and frequently tapped ascites. An elimination of albumin in considerable quantity may cause impoverishment of the blood. There are large albuminurias,—from 8 to 12 grams in twenty-four hours. This last limit is seldom exceeded; we mention as very rare that of 16 grams. I have seen a patient lose 19 grams daily of albumin, reckoned as dry albumin; it was in a case of amyloid degeneration of the kidneys, liver, spleen, and stomach. In these cases we understand that a rapid cachexia is produced, by hypo-albumosis, when the nephritis is accompanied by functional alterations or lesions of the digestive canal.

There are patients in whom the density of the serum falls from 1030 to 1013, consequent upon the absolute want in the blood-plasma of proteid matter, and of a relative hydræmia. There is produced a correlative increase of water, a relative hydræmia, and, besides, often enough, an absolute hydræmia, because there has been retention of water.

The extreme cases belong chiefly to amyloid nephritis, because in such the liver, spleen, stomach, and intestine are diseased. All the organs whose function it is to transform the peptones of digestion into serum-albumin have undergone deterioration at the same time as the kidney. When such a large number of organs is diseased we can scarcely regard all the accidents which happen as due to renal impermeability. We cannot say that there is uræmia, nor even kidney disease; there is a general disease of the organs concerned in assimilation.

Hydræmia is not always caused by the retention of water; it may be produced by diminution in the amount of solid matter. On the other hand, hydræmia may be prevented by attacks of vomiting, diarrhœa, anasarca, in spite of oliguria; then comes thirst, a frequent accident, which introduces as much water as the accessory emunctories can remove. There is then a collection of conditions extremely complex, and all foreign to intoxication; therefore we do not pretend to explain by intoxication most of the accidents of nephritis.

As a consequence of hypo-albumosis there appear œdema, anasarca, and serous accumulations in the large cavities. According to Bartels, the hypothesis of Bright, which regards hydræmia as favorable to the diffusion of serum, is not sufficient. Bartels believes that there is an hydræmic plethora. He calls to his aid the oliguria which generally accompanies œdema. And yet in absolute anuria, such as is produced in the obstruction of the two ureters by calculi, anasarca is exceptional. I do not know how œdema is produced in albuminuria, but the hypothesis of Bartels seems to me to be inadmissible.

In a goodly number of cases we must take into consideration both vascular and cardiac disturbance, but in interstitial nephritis, in which cardiac lesion is the rule, we find little œdema, and in amyloid degeneration, where the heart is normal, dropsy is extreme. Yet some have thought that the hypertrophy of the heart was compensatory to the renal impermeability; at any rate, it may be said that the heart is a dangerous auxiliary, for grave accidents may result from this so-called providential hypertrophy.

We see in certain cases lesions of the kidney, heart, and vessels develop simultaneously; all the vascular system is seized, from the central organ of the circulation up to the finest extremities; and if the kidney can suffer from such a delicate symptom as albuminuria, we have no right to disregard, on that account the sufferings of other organs. We know how modifications of the cardio-vascular system bring about secretory disturbance in the digestive canal, a dryness and a condition of prurigo of the skin, which may be the consequence of a nutritive affection of the terminations of the nerves in the skin. As the result of vascular lesions we also observe hæmorrhages, epistaxis, hæmatemesis, entorrhagias, cerebral hæmorrhage, and purpura.

All this is not allied to uræmia; it is all beyond intoxication, and shows itself when the urine has still a normal density or is raised, and when its quantity is increased, normal, or slightly diminished.

Throwing out of consideration all the foregoing accidents, we ask what remains to cause intoxication? It will be quite legitimate to attribute to it one part only of the phenomena which might supervene when the impermeability of the kidney is such that it can no longer eliminate the toxic substances produced by the organism in proportion to their formation.

Testing the urinary toxicity would give us sufficient information on this point, but it is a method little practiced, and at the bedside we are in the habit of making estimations upon the total quantity of urine passed in twenty-four hours and upon its specific gravity. If the quantity and density remain normal we have the right to say, from these facts, that the kidneys functionate normally. If both are diminished, there is danger of intoxication.

We must not, in this estimation, take for our type the quantity of urine secreted by a healthy man; a sick man ingests and destroys little. The numbers—*e.g.*, of 1350 cubic centimeters as the quantity and 1019 as the density—are too high for a patient; they are only normal in a man who is walking about and eating well. Last, the quantity and the density may balance each other in a certain measure.

However it may be, all the accidents of nephritis of which we have hitherto spoken are produced during a period in which the urine is still normal in quantity and density. Retinitis, amaurosis, inflammation of serous membranes, and phlegmons appear at a period already advanced. And yet there is nothing to show that the retinites are uræmic accidents of the same nature as the respiratory disturbances, or coma and convulsions. I admit that, in individuals who retain their toxic products, all the cells of the organism have a weakened vitality, bordering upon inflammation which has not resolved. But these incomplete phlegmasias, œdema of the glottis, hæmorrhagic and purulent pericarditis, are, at any rate, only accidents farther removed and indirectly due to intoxication. They denote simply a cachectic state, of which poverty of blood and insufficient alimentation are the principal factors.

Yet, after having removed from the category of uræmia all these symptoms, all the accidents that we have just reviewed, we come to others which, in the advanced periods of chronic nephritis or in the course of acute nephritis, directly flow from renal imperfection that has become excessive. Beyond this we enter the domain of intoxication.

We find ourselves in the presence of an intoxication which may be due to one of seven poisons, which analysis of the products of toxicity has revealed to us, or to several among them, associated two by two, three by three, or to all the seven together; finally, water (the elimination of which may be prevented) may play a part in the morbid accidents. It appears impossible that there should be one form of uræmia only. Already clinically there have been described for a long time different symptomatic forms. Perhaps there is a place in pathogenesis for the five following theories, which include (1) cerebral œdema (Traube); (2) urea (Wilson); (3) ammonia (Frerichs); (4) extractive matters (Schottin), and, notably, oxalic acid (Bence-Jones), urochrome (Thudicum), and (5) potass (Feltz and Ritter).

# LECTURE XII.

## PATHOGENESIS OF URÆMIA—DISCUSSION OF THE EXCLUSIVE THEORIES.

**The uræmic period of nephritis is characterized by the appearance of chronic or paroxysmal nervous accidents,—cephalalgia, dyspnœa of the Cheyne-Stokes type, convulsions, coma,—associated or not with disturbances of calorification and with other symptoms of the pre-uræmic period; for example, œdemas.——Clinical observation has established several modes of grouping of symptoms of the uræmic phase while seeking to relate them to certain anatomo-pathological forms.——Every inventor of a pathogenic theory has appealed to bedside observations for a justification of his opinion.——Traube incriminated, as the cause of uræmic accidents, the cerebral œdema which might result from hydræmic plethora. His opinion is wanting in anatomo-pathological proofs, and rests rather upon inadmissable physiological arguments.——Chambrelent and Bois: diminished urinary toxicity in pregnancy.——Wilson invoked excess of urea in the blood. Urea cannot explain accidents in the quantity in which it exists in the blood of uræmics. Injection of urea into the stomach, into the cellular tissue, into the veins after nephrectomy.**

I HAVE shown that many of the accidents called uræmic happen at a period of nephritis in which the retention of toxic products is inadmissible. As long as the urine is of sufficient quantity and has a density high enough, there is no intoxication. The question of uræmia can only be argued from accidents happening at a time beyond that in which imperfection of the kidney has become excessive, such as when it eliminates no longer, in twenty-four hours, the toxic products introduced into the organism or formed by it during this length of time. Then we may see a series of chronic or paroxysmal nervous accidents happen, characterized by pain in the head, dyspnœa of the Cheyne-Stokes type, vomiting, diarrhœa, convulsions, and coma, at the same time as a certain number of accidents of the preparatory period persist. We still find œdemas, which increase or diminish; alterations of temperature; sometimes hypothermia, which may fail and give way to hyperthermia.

The nervous accidents may be isolated or associated; and already, from this point of view, as from that of the coexistence of unusual symptoms and the presence or absence of low temperature, cases of uræmia when observed clinically, seem so

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different the one from the other that we must think of the existence of various and mixed pathogenic conditions. Very likely we have to do not with one form of intoxication only, but with numerous causes, which may be isolated or associated; so that if one explanation holds for one case it does not necessarily hold for others, and a false theory in one case may not be so in others. If we wish to include the whole pathogenic study of uræmia, we must be persuaded that we cannot offer one explanation alone of all the nervous accidents which may appear in the course of disease of the kidney. Besides, clinical observation has endeavored to group a certain number of particular cases, according to their symptomatic resemblances, by calling to its aid pathological anatomy.

There exists a symptomatic form, characterized by early dropsy of the anterior surface, developed a long time ago or just a short time previously. We have seen œdema increasing, the urine becoming less abundant, its density increasing (a greater quantity of solid matter being found in each unit by weight), or remaining the same. The patient has neither diarrhœa, vomiting, nor any other flux capable of carrying away water, and there is oliguria; there is, therefore, retention of water in the organism. The other normal secretions continue; the tongue is moist. We in vain seek for the presence of ammonia in the expired air. In these cases are found reunited all the conditions of hydræmia or of hydræmic plethora. The urine continuing to carry away the total quantity of solid matter which ought to be eliminated by the kidneys, it is impossible to explain, by the theory of intoxication, the accidents which arise. There is, on the contrary, an undoubted accumulation of water in the organism. Thus, the idea has arisen that the accidents called uræmic are due to an accumulation of water.

Traube has actually thought that the consequence of hydræmia was a tendency to the production of œdema, and, notably, to cerebral œdema. Coindet and Odier have seen in this sufficient to explain the development of a ventricular dropsy. According to their manner of viewing the subject, interstitial œdema or ventricular dropsy, by compressing the encephalon within and without, diminishes the space left free for the blood; hence cerebral anæmia involving the production of comatose conditions when the anæmia is especially marked at the level of the convolutions, or convulsions if it predominate in the mesencephalon.

If we wished to furnish, like Traube, a general explanation of the facts reputed to be uræmic, his theory would be false; and it is so in effect, as he has formulated it. Indeed, in the large majority of cases followed up by an autopsy cerebral œdema, ventricular drops, and cerebral anæmia are wanting. And not only has evaporation not demonstrated the existence of a larger proportion of water in the tissues of the brain than normally, but in place of anæmia it is easy to establish congestion pushed to the point of extreme fullness of blood-vessels and to ecchymoses. These are the cases that disprove his theory. But, besides, this must hold good for all cases or its falsity is not demonstrated; otherwise, it remains a pure hypothesis which does not rest upon any foundation of direct observation. It is untrue even as a theory, for a certain number of physiological arguments invoked by Traube are inadmissible.

In a large number of cases we see uræmic accidents produced in patients who are eliminating water in excess; their urine is more than normal in quantity, and they discharge it from the stomach and intestines.

Hydræmia should have, as an effect, œdema; but it would be necessary to demonstrate experimentally this relationship, for neither experimental pathology nor clinical observation confirms it.

Double calculous obstruction, suddenly developed, produces uræmic accidents, at the end of a recognized time, without inducing œdema. Thus is found broken one of the links in the chain of reasoning of Traube.

Richardson has injected into the peritoneum of a dog a quantity of water equivalent to one-fifth of the weight of the animal. He has produced everything but intoxication. He has caused death by septicæmia, rendering possible, thanks to the modifications which the injection had suddenly brought about in the tissues, the escape of some infectious agent from the digestive tube or from without, and which has become capable of producing septicæmia.

But, in what form of disease of the kidneys do we find in the body such an accumulation of water?

Falck has injected the same quantity of water into the veins; he has seen convulsive accidents and death; but these, we might say, from the point of view of experimental pathology, are monstrous operations which are not at all comparable to pathological facts. It is the exaggeration of a legitimate demonstration.

We may inject water into the blood in considerable quantity. Death results from this injection when we have introduced into the blood 122 grams of water per kilogram of animal, in which case the density of the serum of the blood falls to 1007; but the density of the serum of the blood in those the subjects of uræmia falls seldom, if ever, below 1016. In the experiment of Richardson and Falck the blood is nothing more than a diluted blood. There come no longer into the capillaries anything but swollen globules, deprived of hæmoglobin and therefore inactive. How can we compare this excessive hydræmia with the moderate retention of water in the blood which may exist in pathological cases? In absolute anuria uræmic accidents burst forth sometimes before the fifty-sixth hour, when a man has not as yet accumulated more than 35 grams of water per kilogram of his weight. But we know that injections of water only begin to be injurious after 90 grams per kilogram.

It has not only been shown that the viscera may be invaded by œdema. Bartels has proved, at any rate, that pulmonary œdema does not exist in those suffering from uræmia.

Let us accept, however, if you please, cerebral œdema. I am ready for all concessions. But then it will be no longer a question of intoxication. If this œdema has nothing to do with the retention of solid matter it enters into the category of the phenomena which we have previously eliminated from the list of uræmia; they are part of the mechanical accidents of nephritis, and are improperly included among chemical accidents. But, are there any chemical and toxic accidents in Bright's disease?

We can furnish proof—yes, direct proof—of this. Uræmic patients are those whose urine has lost its toxicity. We have seen renal elimination diminish in quantity and the density of urine fall, and we have been forced to believe that owing to the whole of the solid substances being no longer eliminated, the individual was about to become intoxicated. But on the day in which nervous accidents called uræmic appear the urine ceases to be toxic. The whole of the urine of twenty-four hours from a uræmic patient cannot kill a rabbit, nor does it exceed the toxicity of distilled water. And yet, while with 120 cubic centimeters of distilled water per kilogram of animal, used as an intravenous injection, you are in danger of inducing death, with this same dose of certain urines taken from uræmic subjects you will determine no phenomenon, not even the pupillary contraction caused by normal urine.

[Numerous experiments made by later writers have confirmed the statement just made that the urine of eclamptic women loses its toxicity owing to the retention of poisons in the blood and failure of the kidneys to eliminate these by the urine. In a series of researches on the toxicity of urine in pregnant women Chambrelent and Bois found a marked decrease in the toxicity of the urine beginning with the second month of pregnancy, a decrease which they believed to be due to functional hyperactivity on the part of the liver, for should hepatic inadequacy by any means arise the toxicity of the urine invariably increases. So long as the toxicity of the urine is at its maximum the individual is free from the risk of auto-intoxication. In the permeability of the kidney to poisons there is safety.]

There yet remains to be known what is or what are the poisons which determine the toxic and chemical accidents of uræmia. Let us return for a moment to hypotheses. In the first line is placed the old hypothesis of Wilson, which has recently been revived, and according to which the accidents called uræmic would be caused by the accumulation of urea in the blood. It is no longer sufficient to say that the urine of those suffering from uræmia contains less urea. It has been shown that there is in the blood as much as thirty-two times more urea than in the normal state; that in the muscles there is as much as 1.20 grams instead of simply traces of it. I have met with it, among those suffering from choleraic anuria, in the tissues where it is not formed normally. The theory, therefore, would be legitimate save for its demonstration.

Gallois has injected into the stomach, Treitz into the veins, and Richardson into the cellular tissue, large doses of urea. Gréhant and Quinquaud have likewise injected it into the cellular tissue. These last observers have seen toxic accidents. Treitz, who had made injections into the veins, has not observed anything. Hammond practices nephrectomy and then makes an injection of urea,—the animal dies. The experiment of Hammond is repeated by Frerichs, Oppler, and Petroff, and these conclude that after nephrectomy the animals, into which they injected urea, do not die more quickly. This contradiction was so singular that Feltz and Ritter have repeated the experiment. They have at length induced death as speedily in healthy animals as in those upon whom they had performed nephrectomy. They employed urea which they obtained from Germany, so as to have it purer. On analysis this, however, was found to contain sulphate and chloride of ammonia. Ritter began to prepare pure urea himself, and, setting out from the day in which he made injections with this urea, he no longer determined accidents. Such is, perhaps, the explanation of the contradiction between various experimenters.

As for myself, relying upon my own experiments, I say that urea, in the quantity in which we meet with it in the organism, in pathological states, cannot be invoked to explain the accidents called uræmic.

In order to kill a man it would require the total quantity of urea which he makes in sixteen days. But, in double calculous obstruction, suddenly developed, uræmic accidents appear—sometimes at the end of the second day or at the commencement of the third—at the time that man has not yet made the eighth part of that amount of urea which is necessary in order to cause death. During that time, as we know, he has been able to accumulate a sufficiency of other toxic substances capable of bringing about intoxication. Clinical observation is here, therefore, completely in accordance with experimentation in denying to urea the power of producing the intoxication called uræmic.

# LECTURE XIII.

## PATHOGENESIS OF URÆMIA—DISCUSSION OF THE EXCLUSIVE THEORIES.

**Theory of *ammonæmia* (Frerichs). Is the carbonate of ammonia resulting from the breaking up of urea in the blood the cause? Is urea transformed into carbonate of ammonia in the digestive canal? (Brenard and Grandeau, Treitz, Jaksch.) Objection to the theory of ammonæmia as the absolute explanation of uræmic accidents.——Theory which incriminates *extractive substances*; that of Schottin, Scherer, Oppler, Chalvet. *Creatinæmia* of Jaccoud. Examination of the possible action of each of the extractive substances,—uric acid, hippuric acid, creatin, creatinin, leucin, tyrosin, taurin, xanthin, hypoxanthin, guanin. Theory which invokes the coloring substance, urochrome (Thudicum). Element of truth which it contains.**

THE clinical fact of which we are going to seek the explanation is this: The co-existence of nervous disturbances, called uræmic, with a diminution of the solid matter contained in the urine of twenty-four hours,—a diminution proved by the volumetric examination of the whole of the urine of twenty-four hours and the examination of its density.

I have shown that this diminution of solid matter of the urine had for its corollary the retention of toxic material, since I have proved the harmlessness of the urine passed by uræmic subjects.

After this, while reviewing the various hypotheses which have been built upon the nature of the poison or poisons, the retention of which produces uræmic accidents, I have combated the theory which recognizes this poison in urea; not that I deny the toxicity of urea (I admit that of distilled water), but because I am certain that urea cannot be toxic in the dose in which it exists in the blood of uræmic patients.

Urea being thus dethroned, we can conceive how, incapable as it is of causing injury by itself, it may become harmful after having undergone transformation. Frerichs has advanced the theory that the carbonate of ammonia resulting from the disintegration of urea is the pathogenic poison of uræmia; such is the theory of *ammonæmia*. As was said when discussing œdema, some have twisted the clinical aspect, in order to give a symptomatic entirety which would appear to be in accordance with theory. It has been said that a particular form of uræmia shows itself in those suffering from albuminuria without œdema, but having diarrhœa and vomiting and with dry tongue. Then supervene severe eclamptic accidents. The urine is scanty, and of little density. Some may have found ammonia in the blood, and the ammoniacal exhalation of the breath has been sometimes established. Here, then, is a theory which stands well simply as a theory. Yet let us see, for a little, some of the details. One thing alone is convincing in this picture,—the diminution in the quantity and density of the urine. But the retention of ammonia is insufficient to explain this diminution of the density. The presence of ammonia in the urine, although it is denied still by many authors, is really and simply a trace,—especially at certain hours of the day. When I was physician at the Bicêtre, eight years ago, I established the presence of ammonia in the urine after meals composed of roasted meat,—that is, alimentary ammonia; otherwise, these ammonurias consequent upon meals are feeble.

The presence of ammonia in the expired air belongs to a large number of pathological and even normal cases; it is sufficient that there may have been dryness of the throat and of the mouth, owing to diminution of the secretions.

We have met with ammonia in the blood of some who were the subjects of uræmia, but normally we find traces of it in the blood; there is constantly some of it in the blood of cadavera. There is nothing, therefore, to authorize the incrimination of the transformation of urea into carbonate of ammonia. Besides, if urea is transformed into carbonate of ammonia, it is not by the phenomenon of retention,—it is by a fact of faulty nutrition.

But if nothing authorizes the admission of this transformation as the cause of uræmia, here is what authorizes its rejection. When we inject urea into the blood, it is eliminated in its entirety in twenty-four hours, without the ammonia of the urine being increased (Feltz and Ritter). The amount of urea found in the urine exceeds but slightly that of the injected urea; besides, normal urea, owing to its diuretic action and by its bathing the tissues better, leads to the elimination of an excess of urea; but we do not find ammonia in the urine, or not more than in the normal state. Therefore, the theory of Frerichs is wrong.

Bernard and Grandeau, Treitz, and Jaksch have thought that urea may be transformed into carbonate of ammonia, not in the blood, but in the digestive canal, after having passed through the intestinal wall. But the renal path is the natural channel of elimination, and so elective is it for urea that it is all but impossible that it should take any other. Urea is eliminated fifty times more quickly by the kidney than by any other emunctory. If 1 kilogram of blood contains 16 centigrams of urea, 1 kilogram of urine contains 16 grams. But it is the plasma of the blood which delivers the urea, and 1 kilogram of plasma contains 32 centigrams of urea,—fifty times less than the urine contains. Urea, as I have said, passes through the kidney in the ratio of 52, while water is as 1. As regards the other organs of elimination, on the contrary,—through the wall of the stomach, for example,—the filtration of urea is just the same as for water. The liquid secretion contains urea and water in the same proportion as the plasma of blood.

Blood cannot, therefore, carry to the stomach and intestine sufficient urea for its transformation to explain intoxication. In 1872 and 1873 I have shown this fact, apropos of hysterical vomiting, attributed wrongly to ischuria or anuria.

As for invoking the disintegration of urea, in order to explain the presence of ammonia in the digestive canal, it is quite useless. There is enough of it normally, without the intervention of urea. Can we say that ammonia may not play some other part in uræmic accidents? I only say that ammonæmia is not an explanation applicable to the whole of the facts of uræmia, and that neither in the intestine nor in the blood can urea produce ammonia in sufficient quantity to bring about intoxication.

Nevertheless, ammonæmia may be produced in cases of absolute retention by the kidney. Ammonia is toxic, in moderate doses, like potass; it produces convulsions and a great fall of temperature. This symptom, which ammoniacal intoxication produces in the highest degree, is only an accident contingent to certain uræmias. It may be, therefore, that ammonia belongs to the number of toxic substances the accumulation of which in the economy causes accidents, but it is not demonstrated that the uræmic accident can be explained by the presence of ammonia in the blood. We reject ammonæmia as the absolute explanation, while admitting that it may be the key to certain peculiarities, to some of the special symptoms of uræmia, and that it may particularly arise in cases where intestinal fermentation is increased. Hypothermia is produced by normal urine, but once it is filtered through charcoal it loses this property. Urinary ammonia passes through the filter, while the substance which determines hypothermia is retained in the charcoal. The hypothermia of certain uræmias is not, therefore, capable of being attributed to ammonia.

There exists in urine a group of bodies which are not all named, and which are confounded under the title of *extractive substances.* By degrees we recognize the chemical characters of some of them,—so much so that the unknown part of the extract becomes gradually less and less. For a long time, now, have these extractive substances been incriminated by Scherer, Schottin, Oppler, Perls, and Chalvet. In this way has the theory of poisoning by extractive substances originated which Jaccoud has formulated, under the name of *creatinæmia,* without accusing more particularly creatin, except in symbolizing, under this category, the toxic action of all the group.

Clinical observation, which has pretended to give support to the different theories, brings to this its array of observations; but, if we examine the facts cited as bearing upon poisoning by extractive substances,—for example, those of Chalvet, who has demonstrated in these cases the increase of extractive matters in the blood,—we do not see such or such a clinical symptom predominate. It is the picture of uræmia complete in all its forms, with the exception of this form of supposed uræmia in which the urine contains in twenty-four hours a quantity of solids equal or superior to the normal.

In the cases regarding which Chalvet and those who share his opinion have spoken, we see the amount of the extractives, of urea, and coloring matter diminish in the urine; in the blood extractives increase while the toxicity of the urine diminishes, as I have shown. That is true uræmia. Well, let us see what may be, from the point of view of the production of toxic accidents, the action of each of the organic substances taken from this group of extractives:—

*Uric acid* is not toxic in the dose of 0.64 gram per kilogram of the animal. *Hippuric acid,* according to Challon, Feltz, and Ritter, can only become toxic in the quantities formed by the animal in from ten to twelve days. I have injected into the veins of the rabbit hippuric acid, dissolved in water by the help of a little soda, in the dose of 4.59 grams per kilogram of animal, without inducing the slightest toxic phenomena. This inoffensive amount represents nearly the whole quantity which the animal would have required one hundred days to make. *Creatin* undoubtedly increases in the blood of individuals who succumb to uræmia (Scherer, Schottin, Hoppe, Oppler). Is the toxicity due to it? Challan finds it toxic, Testut not toxic. Feltz and Ritter have not been able to kill an animal by injecting into it all at once the quantity of creatin which it excretes in seventeen days. Creatin may, therefore, be incriminated still less than urea; for, if urea can kill when it is injected abruptly into the veins of an animal in the quantity which it would have formed in sixteen days, we do not determine in it, according to my experience, any appreciable toxic accident, by injecting into it the quantity of creatin which it would have formed in seventy-two days. Creatinin, which exists in the blood in such small quantity that it appears doubtful to many physiologists, is formed in the kidney by transformation of creatin. Could it be taken up again by the blood, in case of obstruction to the renal excretion? Feltz and Ritter have proved that the creatinin excreted in six days does not kill, but that death may be caused by the quantity which is excreted in thirteen days. It can, therefore, induce intoxication, if it exist in the blood in sufficient quantity. But it is an energetic base, capable of producing accidents by virtue of its excess of alkalinity. It can only be employed in the form of salts. The chloride of creatinin is hardly injurious; the quantity of creatinin excreted during ten days, and injected, in the form of creatinin chloride, by an intravenous channel, does not hasten death by one minute, in the case of a dog, after nephrectomy. Death has been induced on the third day, as ordinarily (Feltz and Ritter).

*Leucin:* All that water can dissolve of it produces no accident (Feltz and Ritter). The quantity of *tyrosin* excreted in three days by sick men is not followed by any toxic effect. *Taurin,* in the dose of 0.5 gram per kilogram of animal, is without effect. *Xanthin, hypoxanthin,* and *guanin* do not produce any result either.

The *coloring substances* have been incriminated by Thudicum, on account of the feeble coloration of the urine of those suffering from uræmia. We have seen already that normal urine loses the one-half of its toxicity by decoloration; decolored bile is also less toxic. The coloring matters are, therefore, suspected by me from their toxicity point of view; but does not filtration by charcoal remove from the urine any other thing than the coloring substances? I am not right in saying that the coloring substances are the true—the principal—cause of the toxicity of urine. Nevertheless, they belong to the group of those organic substances to which we ought to attribute nearly the one-half of this toxicity. I have tried to estimate the degree of toxicity of one of the coloring substances of the urine, viz., urobilin. Thrice I have made, in the case of a rabbit, an intravenous injection of this substance; thrice the experiment has failed, from want of sufficient quantity of material. I can only say that, if bilirubin kills, after a dose of 5 centigrams per kilogram, urobilin, in a dose of 15 centigrams, does not kill at all.

## LECTURE XIV.

### PATHOGENESIS OF URÆMIA—THE PART PLAYED BY ORGANIC SUBSTANCES AND MINERAL MATTERS IN URÆMIC INTOXICATION.

**Urea represents one-seventh or one-eighth of the total toxicity of urine; ammonia contributes to it a part scarcely appreciable. We can accord to the coloring substances, and others fixed by charcoal, two-fifths of the toxicity; but the sum of all the organic matter represents only two-thirds of the total toxicity. The difference is, therefore, made up by the *mineral matters*.——Exaggerated statements of Feltz and Ritter, who consider them the sole cause of uræmia.——Analysis of the action of various mineral matters. Earthly salts; alkaline salts. Small importance of the salts of soda. Importance of the salts of potass (chloride of potassium; phosphate, sulphate, and phenylsulphate of potass).——Physiological antagonism between narcotizing substances and those of an organic and mineral nature, which cause convulsions. The predominance of coma or convulsions in uræmia depends upon the retention of convulsion—causing or narcotizing substances. Uræmia is a mixed form of poisoning, and due to many causes.**

IN recapitulating the bodies in which we recognize a certain toxic power, we find urea, which would represent one-seventh or one-eighth of the total toxicity of urine; ammonia, which is toxic, but in a fraction which escapes us; those substances which behave in the manner of coloring matters, being, like them, fixed by charcoal, and to which we ascribe two-fifths of the toxicity. Each one of these bodies induces intoxication, and may play its own part; but the sum of all these organic substances only represents two-thirds of the whole toxicity of the urine. What is, then, the difference necessary to complete this totality? There remains to us the *mineral substances* which, according to Feltz and Ritter, would be the exclusive cause of the toxicity. There is evidently fallacy in the statement of these authors, who have made such remarkable researches. They refuse to take any notice of partial or fragmentary intoxications; they do not wish to admit as a toxic agent anything but one substance alone. This is the vulnerable point of their work.

These experimenters, who deny that all the toxic action is due to the organic substances, have yet recognized their toxicity; but they do not take any account of these organic substances, because by them alone they have not been able to produce death, not having carried the injection sufficiently far, and in strong enough doses. In the case of an animal dying within three days after nephrectomy, they have said that the cause of death could only be the substance which kills in a quantity equal to that which is normally excreted in three days. Now, since by the extract of the organic substances of the urine of three days they have not been able to produce death, they deny to the organic substances every toxic action, without wishing to admit that their partial toxicity could be regarded as an explanation of the complete toxicity.

Let us see, however, with MM. Feltz and Ritter, what the mineral substances can do? These are very numerous, but a large number of them can be left out of consideration, on account of their insignificant weight. A man of 75 kilograms eliminates in twenty-four hours 1350 grams of urine, the density of which is 1019. This urine contains 59 grams of solid matter, which is decomposed into 43 grams of organic matter and 16 grams of mineral. These last are composed of 2 grams of earthy salts (salts of lime and magnesia), 4 grams of salts of potass, and 10 grams of salts of soda, including in these weights the acids of the bases. If we state these as being the figures for the composition of a liter of urine, we have:—

| | | | |
|---|---|---|---|
| Solid matter, 44 grams. | Organic, 32 grams. | | |
| | Mineral, 12 grams. | Earthy salts, | 1.50 grams. |
| | | Salts of potass, | 3.00 grams. |
| | | Salts of soda, | 7.50 grams. |

The whole of the earthy salts do not come out well in experiment, on account of the difficulty which there is in maintaining them dissolved in the blood-plasma by intravenous injection. I cannot, therefore, say anything about them. Besides, they are in small quantity in the mineral mass. The alkaline salts on the contrary, are very soluble. They are of large quantity, and deserve our attention.

The salts of soda seem the more important on account of their weight. In reality they have only a feeble toxicity. Chloride of sodium kills 1 kilogram of animals in the dose of 5.17 grams; but chloride of sodium is the most toxic of the salts of soda of the urine. The soda of the urine of twenty-four hours would kill, at the outside, 2 kilograms, while this quantity of urine kills 30.

It is otherwise with the salts of potass. They are occasionally present in large quantity,—3 milligrams per cubic centimeter of urine. Forty to sixty cubic centimeters of urine being toxic (the mean 45), the quantity of urine which kills one kilogram of animal would contain nearly 13 or 14 centigrams of salts of potass. This would be nearly a sufficient quantity if all the salts of potass were represented by chloride of potassium; but there are the phosphate, sulphate, and phenysulphate of potass, which do not have the same toxicity. The chloride of potassium is the most toxic; it kills in the proportion of 18 centigrams per kilogram of animal. But the phosphate of potass only determines toxic accidents after a dose of 26 centigrams. With the phenylsulphate we have seen toxic accidents, but not death. These differences of toxicity explain to us that the mixture of the salts of potass gives a less toxicity than the chloride of potassium.

Like Feltz and Ritter, I have destroyed the organic matter of urine and dissolved the mineral substances, and I have noticed that frequently, contrary to their statements, the salts of potass contained in 50 cubic centimeters of urine do not induce any accident, but that accidents arise if we take the salts of potass contained in a double quantity of urine. In order to kill there is required sometimes a quantity of potass double that which the usual quantity of urine causing death contains. Besides, this quantity of potass kills in quite another way, viz.: with convulsions; whereas normal urine, taken during the height of the day, does not induce convulsions. In death by potass the heart is arrested; this organ continues to beat, however, when it is urine which has caused the poisoning. A normal, decolored urine which still contains nearly all its potass does not kill, even when we increase the dose by one-half, and then it kills without convulsions; in spite of the larger dose, the action of potass remains obscured.

We have already spoken of these toxic associations which exist in urine. The convulsive substance insoluble in alcohol, when added to that which is soluble in alcohol, does not give rise to convulsions. It is the result of a physiological antagonism. A substance which determines convulsions is neutralized by another organic substance which produces narcosis, and this association of the two hinders the appearance of convulsions. There is an antagonism between the narcotic substances soluble in alcohol and the convulsive substances which are insoluble; a possible antagonism, too, between the first and potass. The equilibrium resulting from the antagonism between these various substances may be broken by increasing either the potass or the convulsive organic substance. There are pathological urines which, though decolored, retain their convulsive power; this is perhaps due to the potass. Convulsive urines are especially febrile urines, since there is suppression of alimentation and an increase of cellular destruction.

The diminution of alimentation does not introduce more potass into the economy; it diminishes the totality of the mineral salts. But the increase of disassimilation augments certain nitrogenous substances, and particularly potass, by destroying the mineral framework of the cells. Also, whereas potass only represents one-fourth of the whole mass of the mineral substances, we find potass present in quantity at least equal to the soda. If the urine becomes scanty, if, instead of 1000 grams, the secretion falls to 500, admitting the specific gravity to be equal or higher even than the normal, the quantity of mineral matter which it carries away may be equal to the normal, per liter, but not for the twenty-four hours; the emunction falls to one-half or two-thirds of that which it ought to be and there occurs in the organism an accumulation of mineral substances, particularly potass. This may then become a cause of intoxication, for the substances which are antagonistic to it in the normal state no longer suffice to neutralize its convulsive action. We know that, in uræmic phenomena, there may be, in certain conditions, a predominance of the action of potass, which may represent two-thirds of the toxicity, instead of one-third.

The study of the accidents which arise from intoxication by potass leads up to the denial to it of the rôle of its being the sole cause of uræmia. There are summed up in this word convulsions and death in opisthotonos; but we observe neither contraction of the pupil, diuresis, low temperature due to diminished calorification, nor salivation. All the salts of potass kill with stoppage of the heart, which urine does not.

Thus I admit that potass is toxic, but not that urines are rendered toxic by it alone. If we seek in clinical facts some reasons for or against the exclusive pathogenic rôle of potass, we find in uræmia reasons to reject the affirmation. First, we must show that in those suffering from uræmia there is an accumulation of potass; but observers who have believed that they have found this in excess have estimated their dosage upon the total quantity of blood. Now, what is toxic in the blood can only be what is in solution in the plasma; what is held as a constituent part of the living cell by force of tension cannot take any part in toxic actions. There is in serum only traces of potass. In the researches, otherwise insignificant and contradictory, which have been made upon the variations of potass, we have taken notice of the serum and of the corpuscles, which are so richly provided with and are so strong in their affinity for it. Suppose even that there is an accumulation of potass in the blood-plasma; this would not explain uræmia, in which there are only convulsions; it would not explain the subjective symptoms which precede those or accompany them,—narcosis; uræmic coma; pupillary contraction, which is a prominent phenomenon in uræmia (a circumstance impressed upon me during the course of the last cholera epidemic). All these symptoms intoxication by the whole of the substances of the urine explains, but not by potass. We can appreciate the relative toxicity of the principal mineral substances of the urine from the following table, which I have taken from experiments made in common with M. Tapret. For Table of Substance, see next page.

If we apply these facts to the results of the analyses of urine of man, we arrive, by means of calculations, of which I shall spare you the details, at the following results:—

One kilogram of man eliminating in twenty-four hours a quantity of urine capable of killing 461 grams of animal, the proportional part of the mineral matter in this toxicity may be indicated as follows: potass kills 217 grams; soda, 30 grams; calcium, 10 grams; magnesia, 7 grams. The whole of the mineral matter kills 264 grams. On the other side, urea kills 63 grams. There remains to be destroyed 134 grams. We know from other experiments that normal urine leaves behind in charcoal one-third of its toxicity; that charcoal, consequently, retains matter which must be capable of killing 154 grams. Among these substances fixed in charcoal there is one-sixteenth of the total potass; this fraction of potass would kill 14 grams. The organic substances capable of being fixed by charcoal would therefore be capable of killing 140 grams. This figure passes by 6 beyond the 134 grams which remain to produce intoxication. That is due to errors inherent in all these estimates; the cause of it may be in the charcoal being able to fix a part of the urea or some mineral matter other than potass; it may finally be explained by the urine containing poisons which are antagonistic, —a fact which we have placed beyond doubt.

We may say that 1 kilogram of man eliminates in twenty-four hours organic matter, capable of being fixed by charcoal, which is able to destroy at least 134 grams of animal. These substances (coloring, extractives, or alkaloids) represent 30 per cent. of the total toxicity. It is to these substances, still undetermined, that hereafter the effort of chemistry should be directed. We know of them only what physiology has taught us,—one contracts the pupil, another is convulsive, and the third lowers the temperature. Chemistry will also have to isolate, in the alcoholic extract, the narcotic substance and the salivating, which is perhaps toxic. I have thought that the alkaloids will

| NAME OF SUBSTANCE. | Index of Solution. | Quantity of Substance Necessary to Kill One Kilogram of Animal. |
|---|---|---|
| Chloride of potassium | $\frac{1}{150}$ | 0.180 gram. |
| Sulphate of potass | $\frac{3}{200}$ | 0.181 gram. |
| Phosphate of potass | $\frac{3}{200}$ | 0.263 gram. |
| Chloride of sodium | $\frac{1}{10}$ | 5.17 grams. |
| Sulphate of soda | $\frac{1}{10}$ | 9.00 grams. |
| Phosphate of soda | $\frac{1}{10}$ | 6.00 grams. |
| Chloride of magnesium | $\frac{3}{200}$ | 0.463 gram. |
| Sulphate of mágnesia | $\frac{3}{200}$ | 0.542 gram. |
| Chloride of calcium | $\frac{3}{200}$ | 1.011 grams. |

only explain a very small portion of the 30 per cent. of the toxicity attributable to undetermined bodies.

In any case, we have come to this conclusion: It is that the whole of the mineral substances reckon, at the most, as 57 per cent. of the urinary toxicity, and that potass explains, at the most, 47 per cent. of this toxicity. Thus, uræmia comprises various and multiple intoxications, to which are attributable various symptoms. It is a mixed poisoning, not by urine (as one calls it by misapplication of words), but by what should have become urine; for the accidents from the retention of urinary substances are not those from the reabsorption of urine. The sources of uræmia are: disassimilation, a certain number of secretions, alimentation,—especially the alimentary mineral substances,—and, last, intestinal putrefactions. The knowledge of these origins of uræmia furnishes, as we shall see, valuable indications from the point of view of treatment.

# LECTURE XV.

## THE THERAPEUTIC PATHOGENESIS OF URÆMIA.

*Résumé* of the pathogenesis of uræmia considered as a complex intoxication and due to poisons resulting from disassimilation, furnished by alimentation, the biliary secretions, and intestinal putrefactions.——The renal emunction, having become insufficient, may be supplemented by other apparatus,—the skin and lung?——Baths of hot and dry air; vapor baths. Sudorific medicaments. These methods have the fault of diminishing the renal secretion.——Means destined to arouse the renal function, either by reducing congestion of the kidneys (revulsives, cupping, sinapisms) or by accelerating reflexly the renal circulation (utility of dry cutaneous friction). Action of medicaments called diuretics (caffeine, digitalis). Indications, counter-indications, and management of digitalis in nephritis. Cold injections as a diuretic; cool drinks. Urea as a diuretic medicine.——Can we supplement the kidney by utilizing, as an emunctory, the mucous membranes of the digestive canal? Vomitings: their inconveniences. Purgatives: the dehydration of the tissues which they produce may become dangerous.——Of bleeding: it removes from the blood one-sixteenth of the extractive material which the urine ought to throw out. A bleeding of 32 grams removes as much poison as 280 grams of diarrhœic liquid, and as 100 liters of perspiration. Utility of bleeding supported by clinical experience. Its formal indication in acute curable nephritis. Its employment owing to its being the best and a rapid expedient in the terminal uræmia of chronic nephritis.——Antidotes to uræmic poisons. Inhalations of chloroform. Action of chloral. Bromide of sodium. Traditional and pathogenic therapeutics. Milk regimen to diminish biliary secretion and to prevent putrescible intestinal residues. Charcoal as the means of fixing the coloring matter of the bile. Interdiction of roast meat, aliments rich in extractive and mineral matter, soup. Diet composed of milk, white of egg, cheese, boiled meat. Disinfection and intestinal antisepsis with iodoformized charcoal and naphthalin. Agreement between the means which experiment has ratified and those which are the outcome of a study of pathogenesis.

I REGARD uræmia, then, as a complex poison, to which, in unequal proportions, *all* the poisons introduced normally into the organism or found therein physiologically contribute, when the quantity of poison formed or introduced in twenty-four hours can no longer be eliminated in the same time by the kidneys, which have become scarcely sufficiently permeable. This view, the legitimacy of which, I think, I have experimentally demonstrated to you, differs, to a certainty, from the old doctrines and even from those which still prevail to-day, since each one of them endeavors to attribute to the action of one substance alone all the accidents called uræmic. Between the best of these opinions—that which, self-recommended by the name of Schottin, incriminates the whole group of extractive substances, an opinion which M. Jaccoud designates under the theory of creatinæmia—and that which I have proposed there is still this difference, viz.: that Schottin and the partisans of his theory have only regarded as toxic agents the substances which originate from disassimilation; but to me this is only one of the sources of the production of the toxic bodies, and it is necessary to add to them the poisons furnished by the biliary secretion, alimentation, and intestinal putrefactions.

The pathogenic theory which I admit is, then, more comprehensive than its predecessors. Uræmia is to me, I repeat, intoxication by *all* the poisons which, normally introduced into or found in the organism, ought to have been eliminated by the renal path, and are prevented from being so by the impermeability of the kidneys.

Such a conception has led to therapeutic views which appear to me not to be deprived of interest. But before approaching them I ought to treat the question of the possible supplanting of the kidney by other eliminating organs. We have really, for a long time, thought, in cases where the renal apparatus fails to accomplish its depurative acts, of causing the kidney to be supplanted by other organs, such as the skin and lungs. Thus we have given to those suffering from uræmia baths of hot and dry air; we have proposed by this means to introduce, at each inspiration, a certain quantity of dry air, which, expelled during expiration ladened with moisture, removes in this way water from the organism. We have also tried to induce deprivation of water from the economy by increasing the perspiration, either by administering vapor baths or by the employment of sudorific medicines, such as jaborandi. In all these cases we certainly remove something from the blood, but not, unfortunately, that which is toxic. We, perhaps, remove from the economy certain toxic substances which ought normally to leave by the skin, but not those which the kidney is charged with the duty of eliminating. What we specially remove from the organism by this means is water. The inevitable result is diminution of the quantity of urine; and it is difficult for me to admit that this diminution of urine is a useful result in the case of patients whose urine is already diminished, both as regards quantity and specific gravity.

The question might be more logically raised when it is proposed to increase the secretion of urine by various means. Sometimes we have attempted to diminish the congestive state of the kidney, either in acute diseases or in cases of congestive exacerbations arising in the course of chronic affections of this organ, by means of revulsive (wet or dry cupping, leeches, sinapisms). Sometimes we are obliged to stimulate the nervous system by irritating its cutaneous branches by friction, in order to obtain, in a reflex manner, a quickening of the renal circulation and consequently an increased secretory activity of the kidney. I am convinced that, in many cases, cutaneous friction increases urinary secretion. We have demanded the same result for certain medicines, caffeine and digitalis especially,—means differing from the preceding, since they are applied to the central nervous system. Apropos of digitalis, I cannot refuse to tell you that this medicine ought not to be indifferently employed at all periods in diseases of the kidney. When the function of the kidney is impeded it is prudent to use only with extreme caution certain medicines. When the impermeability of the kidney has become such that it ceases to have the power of eliminating toxic substances formed by the organism, there is then retained the medicinal substances; the kidney is as impermeable for therapeutic poisons as for natural poisons, and the employment of toxic medicines, in similar cases, has no other effect than to bring about an association of medicinal intoxication with a uræmic.

Digitalis succeeds, however, in certain cases of Bright's disease, in increasing the quantity of urine, but it is chiefly so when there are cardiac disorders associated with disease of the kidney, and when this organ has not become very impermeable; at a period more advanced we ought to dread the action of digitalis. I do not say that it is absolutely necessary to renounce it, but it is necessary to watch the administration of it very carefully. Prudence, moreover, does not consist in using small doses only; we must employ, on the contrary, sufficiently large doses,—doses that run the risk of being toxic,—without which we would not obtain any result; but these doses ought to be sufficiently small so that we may have time immediately to suppress the administration of the drug if there appear signs of intolerance, nausea, or vomiting. It goes without saying that digitalis is inapplicable in that form of uræmia which is characterized clinically by gastro-intestinal accidents.

There are yet other means of increasing the quantity of urine. We may propose the displacement of a part of the mass of blood, which is in relative stagnation in certain parts of the vascular system, and to throw it into the general circulation, in order to increase the pressure within the vessels of the kidney. Between the arterial capillaries of the abdomen and the liver is found quite a considerable mass of blood accumulated in the portal system and in the hepatic and splenic parenchyma; we may throw that reserve, nearly stagnant, into motion in the general circulation; we may empty, in a word, the portal system, in order to augment the general arterial tension and, in consequence, stimulate the renal function to activity. This result may be obtained by the introduction of cold water into the abdomen, by the employment of cold injections. I have seen, in certain cases, a grave anuria disappear by the use of cold injections; it is therefore a means we ought not to neglect. We may administer cool drinks, which, besides the stimulation which they impress upon the contractility of the abdominal vessels, will induce absorption of a certain quantity of water, in order still to increase diuresis. Among the liquids which it is usual to prescribe, milk is one of the most powerful medicaments which we can oppose to uræmic accidents, and not only to albuminuria. Its advantages are numerous, as we shall see.

We can also utilize as a medicament a body which has been considered, until to-day, a poison, and which is capable, more than any other, of encouraging the secretion of urine. I am now speaking of urea, to which we certainly cannot attribute the accidents of uræmia, and which, on its own side, even combats them by forcing the renal barrier. In animals urea has been experimentally demonstrated to be a diuretic. In a healthy man, ingested by the gastric mucous membrane, it has not appeared to increase the quantity of urine. It would therefore remain to be determined whether, in a sick person, by subcutaneous injections of urea, we could succeed in increasing the urinary secretion. I have undertaken in animals, and more lately in men, experiments bearing upon this point. In a patient with Bright's disease, the subject of a cardiac affection, I have once seen the subcutaneous injection of urea induce a diuresis of 7 liters in twenty-four hours; but I ought to say that in the renewed relapses of oliguria in this same patient the injection of urea has failed, as has also, at other times, the administration of digitalis, which some weeks previously had abundantly induced diuresis.

I have established that the skin and the lung cannot vicariously aid the kidney which has become incapable of accomplishing its task of elimination. But, have other emunctories the power? Or, at least, can we not utilize as emunctories large mucous surfaces, such as that of the digestive canal, the stomach, and intestine?

For a long time we have combated uræmia by inducing vomiting. We have sought to imitate what occurs in certain cases of uræmia in which vomiting is frequent; it is therefore proposed to provoke a secretion of extractive matter from the surface of the stomach. It is not shown that the vomiting notably increases the gastric secretion. It has, on the contrary, two evident inconveniences: it produces two effects,—lowering of arterial tension and, in consequence, diminution of renal secretion; and increase of the cutaneous secretion, which further diminishes the renal secretion. Besides, some have quickly given up this practice, and have had recourse to the intestine, in which they have provoked hypersecretion by drastic purgatives. Purgatives have been employed for a very long time, in accordance with theoretical views. It is upon the theory of Wilson that physicians have relied, who have wished, by means of purgatives, to remove urea from the blood; but the intestinal secretion has no elective action upon urea; it only removes urea from the blood in the proportion in which it is found in the blood-plasma. If the serum of blood contains, per liter, 32 centigrams of urea, the liquid which exudes into the intestine under the influence of purgatives contains exactly 32 centigrams of urea per liter.

On the other hand, if we remove one liter of water from the blood by the intestinal tract, it is simply a liter of water less that will pass away by the renal path; but this liter of water, eliminated as urine, could have removed fifty times more urea. In addition, we know that the theory of Wilson is wrong, and that urea is not the cause of the uræmic accidents.

Let us see what is the composition of the substances eliminated by purgatives, only considered as poisonous. Purgatives remove from the blood, in the first place, water; they dehydrate the blood and, consequently, the tissues; this dehydration, perhaps, causes a diminution of œdemas and effusions into serous cavities; this will remove, perhaps, water from the cells and, along with this water, a portion of toxic material. But there will only result from this a favorable effect if we immediately restore to the tissues the water which we have just removed; otherwise we shall have only displaced the poison by making it pass from the cells into the plasma; after dehydration it is necessary to bring about immediate hydration. This is a dangerous game; we are never sure of being able to graduate at will these alternatives of subtraction and restitution of water from the blood and tissues.

Nevertheless, I do not wish to proscribe a method in favor of which clinical experience seems to have decided for a long time past. Diarrhœa does not remove urea from the blood, but it removes poisons from it. In an adult, in good health, I have, for six consecutive days, measured the urinary toxicity, in periods of four hours. The curve of the toxicity is reproduced each day, regularly and always at the same time. But I have established a disturbance coincident with a diarrhœa. During the four hours coincident with this diarrhœa, urinary toxicity had undergone notable diminution. I have thought that the poisons which were then wanting in the urine had been carried away by the intestinal fluid.

We have until now only discussed means that are injurious or uncertain. What is thought of bleeding? What happens when we remove blood from a uræmic? In removing 32 grams of blood you remove from it 50 centigrams of extractive substances; the daily elimination by urine is 8 grams; you, therefore, in this way, remove one-sixteenth of the extractive substances which the urine ought to carry away. This result is not insignificant; for, if the kidney ought to remove in one hour these 50 centigrams of extractives, and if the convulsive or comatose accidents resulting from this nonelimination can kill the patient during this hour, the bleeding which you induce may save the life of the patient, by removing, for the moment, from him, the excess of toxic material which causes the development of fatal accidents.

In any case, it is certain that we remove from the economy more extractives by bleeding than by any other channel, the renal tract excepted, *for a bleeding of 32 grams removes from it as much as 280 grams of a liquid diarrhœa does, or as 100 liters of perspiration.* Besides, it is not only 32 grams of blood—the quantity drawn by two leeches—which we have removed in similar cases. Abercrombie, Marshall Hall, Rayer, and many others in addition have employed copious bleedings for uræmic accidents, and they have seen patients cured who were assuredly threatened by death. It is chiefly in acute curable nephritis, such as scarlatinal nephritis, that bleeding finds its formal indication when uræmic accidents arise, for in these cases the renal malady only demands cure when the patient does not succumb to the fleeting attack of uræmia. In these cases, therefore, it is obligatory to practice bleeding, not only because it is theoretically legitimate, but because, practically, it has been shown to be useful.

On the contrary, in chronic diseases of the kidney the utility of bleeding is doubtful. We cannot incessantly go on bleeding a patient with uræmia whose kidney is definitively and irrevocably diseased; we should only hasten death by impoverishing his blood. There is scarcely, therefore, cause for practicing bleeding in the terminal uræmia of chronic nephritis, except once, viz.: at that moment when accidents threaten immediate death, and when there is no other hope than of delaying for a little the fatal termination. Since, in the majority of cases, we cannot derive great benefit from bleeding, we have thought of employing antidotes capable of opposing their physiological effects to those of the poisons which have induced the uræmic attacks.

Inhalations of chloroform have been successful, especially in this particular intoxication which singularly resembles uræmia, viz.: in the eclampsia of lying-in women. The evidence of their utility has not been so great in the uræmia of nephritis. In every case they find their application only in the convulsive form, and, of course, we cannot think of them for the comatose form. It is also for the convulsive variety that the action of chloral should be reserved, of which we do not otherwise know what is its exact value in these cases. Bromide of potassium, which has also been proposed, ought to be rejected at once; for it can of itself determine intoxication by the potass which it contains. If we wish to treat uræmic convulsive accidents by bromide preparations we should use bromide of sodium; but never should we employ, in uræmia, *any salt of potassium,* no more the bromide of potassium than the nitrate. Under other conditions we would replace them with advantage by the bromide and nitrate of sodium, which are just as active therapeutically and forty times less toxic.

That is, therefore, the therapeutic program for uræmia, such as our predecessors have bequeathed to us. Among all these means, what of worth remains? Certain diuretic agents,—first, such things as milk, and bleeding for certain cases. Yet perhaps something else might be done for these uræmic accidents by applying the *pathogenic therapeutics* which I have been trying to put in favor during the six years that I have lectured. There are, perhaps, therapeutical indications to be derived from the knowledge we possess of the sources of the accumulation of toxic substances in the economy,—disassimilation, the secretion of the liver, alimentation, and intestinal putrefactions. Let us see if we cannot act upon one or other of these sources of intoxication, so as to exhaust or diminish them.

Can we delay disassimilation? Is there any indication for administering those substances which have the reputation of diminishing the exchanges of nutrition, and which have been called the medicines that save wear and tear: *e.g.,* arsenic and valerian? It would be quite useless. Disease itself has produced this arrest of disassimilation. The accumulation of toxic substances has checked the condition of osmosis; an equilibrium of tension has been established between the fluids,—intracellular and extracellular; the circulation of matter through the cell no longer goes on, except imperfectly; combustible substances and the heat-producing agent, oxygen, no longer enter, but with difficulty, into the conflict,—so little that we see the temperature fall, an evident proof of a check given to nutrition. The temperature, taken in the rectum, may fall to 30 degrees. The disease itself has gone beyond the point wished for in our calculations. It is useless, then, to think of further impeding oxidation, whose insufficiency may, by itself alone, cause death. I go farther: those things which are especially toxic are the products of life without oxygen. Increase the free oxygen, and you will only moderately increase disassimilation, but the products of this disassimilation will be much less toxic. I have seen exposure in compressed air diminish by more than one-half the urinary toxicity. It is, therefore, rational to adopt the practice of Jaccoud, who speaks highly of the inhalations of oxygen in the treatment of uræmia.

What can we do to combat that source of poison which is resident in the biliary secretion? We can first diminish the quantity of bile secreted. A means used empirically, and which is excellent, is milk, when it is well digested, for if it is not absorbed it purges and increases the biliary secretion. But when the digestion of milk is perfect constipation is established, and the dry and hard fæcal residue which it leaves contains almost no biliary pigment. We can also expel bile, when it has been formed, by washing it out by the help of certain neutral salts, whose action is limited to making it force its way rapidly through the intestinal contents as far as the anus. You will avoid, in every case, the potass purgatives,—soluble cream of tartar and the salt of Seignette. But in bile the greatest part of its toxicity rests in the coloring matter. We have proof that decolored bile is much less toxic. We have the means of decoloring bile in the digestive canal by administering charcoal in sufficient quantity.

We can diminish the toxicity which is resident in food sources by diminishing, from this point of view, chiefly their mineral substances,—*e.g.*, potass, which contributes a very important share in the production of intoxication. We will choose, for uræmic subjects, food that is quickly digested and absorbed, and which will also have the advantage of not handing over to the agents of intestinal putrefaction undigested and easily putrescible material. We will search for foods not rich in extractives and in potass. We will, then, avoid meat and, as we have done, empirically, for a long time, we will choose milk, which is slightly rich in potass, and which has proved itself satisfactory, from so many points of view, in the treatment of uræmia. We will add to this the white of egg, and, in case of need, cheese—which no longer contains the soluble mineral matter of milk—and boiled meat; but we will interdict soup.

Finally, a very important indication is to prevent intoxication caused by the products of intestinal putrefaction. We ought to endeavor, first, to admit only a small quantity of putrescible matter into the digestive canal, so that the digestive residue may form solid masses, presenting at the point of contact with the absorbing mucous membrane only surfaces that are hard and not extensive. The pasty residues incessantly mashed by the intestines, on the contrary, successively allow of the absorption of the poison contained in their superficial and deep layers. Milk food, when it is well tolerated, which is the rule when milk is ingested in small quantities and well broken up, produces the desirable result; that is to say, fæcal matter scanty and solid. Thus, from whatever point of view we regard it, milk is opposed to all sources of intoxication.

We can still fix the toxic products of intestinal putrefaction so as to prevent their absorption. Charcoal gives us the means of doing so. We may even oppose putrefaction itself by inducing intestinal antisepsis. We possess, in the association of iodoform in charcoal, and in naphthalin, means which theoretically permit us to practice this thoroughly. Salicylate of bismuth may be employed for the same end, and, if we were afraid of the passage and accumulation in the blood of the small quantity of salicylic acid absorbed, we might substitute for it the subnitrate. In fact, my colleague, Dr. Tapret, has applied this theoretical idea to the treatment of uræmia, and he has thrice seen uræmic accidents disappear when intestinal antisepsis had been induced. I myself have seen in one case formidable uræmic dyspnœa disappear within twenty-four hours after the administration of naphthalin. The patient, who was diabetic, succumbed later on to gangrene, but, to a certainty, he would have been dead more quickly from his uræmia. These are only four cases, but they are encouraging, especially when we think of the small number of therapeutic means at our disposal for treating uræmia.

Thus, to resume, diuretics (and, in the first place, milk: milk as food), intestinal antisepsis, bleeding for accidents immediately threatening, and, finally, inhalations of oxygen,—that is the treatment which experience has confirmed. It is also that which arises naturally from the conception of the disease, which we have admitted.

# LECTURE XVI.

## TRANSITORY OR ACUTE AUTO-INTOXICATION OF INTESTINAL ORIGIN—INTERNAL STRANGULATION AND CONSTIPATION.

**Increase of the quantity of poison contained in the digestive canal when there is an augmentation of the activity of normal fermentation. Symptoms and signs of the increase of acid fermentation and of putrid fermentation.——Parallel relation between the increase of intestinal fermentation and increased toxicity of urine. Poisons which are found in the intestines and which pass into the urine. Phenol, indol, and indican; cresol. Substance which gives a claret color to urine after the addition of perchloride of iron, but which is not acetone.——How the organism is protected against poisons derived from the intestines. Part played by the liver from the point of view of the arrest and destruction of putrid poisons. Toxicity of indol. Experiments of Schiff and of G. H. Roger.——Utility of hardening the intestinal contents. Rôle of auto-intoxication of fæcal origin, in internal strangulation and the morbid states called intestinal septicæmia (Humbert). The two periods of constipation: constipation with retention of liquid matter causes symptoms of intoxication, and hardening of the substances renders the second period of constipation less harmful.**

WE know that the poisons contained in the intestines, also those which come from food, bile, or putrefaction, enter, on the one hand, into the complex intoxication called uræmia. We can, therefore, understand how, if the quantity of poison increases in the intestines, an intoxication becomes possible; also that disassimilation does not hand over to the blood a larger amount of toxic material when the kidney remains permeable.

To-day we are going to study intoxication by reabsorption of substances contained in the digestive canal, without the presence of other pathological states. Experiment has proved to us that the toxicity of the intestinal contents is mixed, and has revealed to us its various sources. Let us recall these sources:—

1. Foods—even the most inoffensive in appearance—and the flesh of muscles are toxic, particularly, on account of the mineral matter and potass principally. We have shown this by injecting aqueous decoction and the alcoholic extract of meat.

2. Bile contains poison. The eight hundred or one thousand grams of bile which are poured each day into the intestines of an adult of average weight are toxic on account of the coloring matters principally: *e.g.*, bilirubin, and also other sub-

stances: some known,— such as the biliary salts,—others unknown.

3. Putrefaction which occurs in the alimentary residues develops poison. The extract of 2.5 grams of putrefied meat is sufficient to kill.

4. Finally, we have learned that fæcal matter is toxic; that this toxicity is due chiefly to potass and ammonia; and, on the other hand,—and this represents about one-fifth of the total toxicity,—to the union of organic principles, in which are included alkaloidal substances.

Thus, the paths are prepared for the study of intoxication of intestinal origin, since we know that, in normal conditions even, there is material for intoxicating, also of ascertaining what proportion each of the poisons inclosed in the intestines bears to the toxicity of the whole.

We shall now see how, under normal conditions, the contents of the intestines may become more toxic, and how, even with a kidney functionally free, if the production of toxic material is accidentally more abundant, it may yet accumulate in the blood in a proportion capable of causing symptoms of intoxication to arise. When fermentation has become more active in the whole length of the digestive tube, we see produced a succession of phenomena truly characteristic. The unusual development of gas determines abdominal meteorism and tympanites, which may be from the stomach or intestines, or it may be at once carried to the stomach or intestines. The disengagement of gas reveals itself by eructations, preceded by burning sensations in the stomach, or accompanied by pyrosis in the œsophagus and pharynx. It may induce acid vomiting, the acidity of which is most frequently due to acetic acid,—rarely hydrochloric. The acidity of the mouth may cause changes in the teeth. The contents of the intestines, which have become abnormally acid, may not only provoke diarrhœa, by irritating the mucous membrane, but irritate also the skin outside the rectum, as witness the erythema of the buttocks in the acid dyspepsias of infants. An acid reaction is substituted for the normal of the intestinal contents. We notice changes in the color of the stools: bile is expelled, with a green color. The production of sulphuretted hydrogen is diminished. Certain substances, administered with the view of arresting the diarrhœa, such as bismuth, give no longer to the stools a black color, for there is no longer formed sulphide of bismuth. These are the external signs which indicate, even to the naked eye, the production of acid fermentation in the digestive canal.

When fermentation of a putrid character predominates, there is produced rather an excessive disengagement of sulphuretted hydrogen, ammonia, and sulphate of ammonia, which reveal themselves to our senses by the odor of the gas expelled.

Parallel to these objective phenomena there exist those of a subjective character, among which the most ordinary are fatigue, depression, headache, buzzing in the ear and deafness, disturbances of sight, and vertigo. With a kidney acting well things may not go further; but, if the renal emunction is insufficient, we may see developed a fraction of uræmic intoxication through simple exaggeration of intestinal fermentation. If, for example, abundant vomiting has caused oliguria, we may have coldness established, paralysis of the vessels of the skin, cramps, convulsions, coma, paralyses, death even, while the kidney may not be really diseased. It will be sufficient for the development of such accidents that the quantity of toxic material introduced into the blood should exceed the activity of the kidneys charged with the function of eliminating it.

From proof of the preceding facts, we can already conclude that the quantity of urine passed is very important in the intoxication of intestinal origin; that variations of urinary toxicity may be, in similar cases, the measure of the degree of intoxication; and that we should find, under the influence of intestinal fermentation, an increase in the toxicity of the urine. I have known that in a large number of diseases it is thus. If I suppress intestinal fermentation, I cause the toxicity of urine to diminish; I cause it to diminish, but not to disappear, since I only suppress one of the natural sources of its toxicity. I can diminish the toxicity of urine either by neutralizing the products of putrefaction, by the aid of charcoal, which prevents their absorption, or by preventing putrefaction itself, through causing intestinal antisepsis, by means of iodoform and naphthalin. I have thus proved the reality of the passage of a larger quantity of toxic material from the intestines to the kidney in cases where there has been an increase in intestinal fermentation.

This proof had already been given formerly by chemistry. In my experiments of 1882, in which I only occupied myself with one class of toxic agents,—alkaloids,—I had shown that they increase in a parallel manner in the fæces and in the urine. I had concluded that the organism is, from this fact, under the risk of a constant menace of intoxication. Other observers had preceded me in this path. Städeler, in 1848, had found phenol[1] in the urine, without drawing any conclusion from it. In 1877 Baumann found phenol in fæcal matter; we must really admit that this passes from the digestive tube into the urine. In 1826 Tiedemann and Gmelin discovered in the duodenum a substance which gave a red color with chlorinated water,—indol. Braconnot, without noticing in his discovery any relationship with the preceding, has shown in the urine the existence of a certain substance of a different color,—cyanurin,—which is indican derived from indol. In 1872 Jaffe made a subcutaneous injection of indol, and he saw that indican appeared or increased in the urine. The indol, therefore, which is formed in the fæces is the cause of the urinary indican.

These early experiments are the source of all that have been made since then. A very convincing experiment is that of Senator. He seeks for indican in the urine of the newly born, and he does not find it; he analyzes the meconium, and does not find indol therein. Nothing is better shown to-day than the parallel relation betwen the increase of indican in the urine and indol in the fæces. That is to say, variations of urinary indican according to the activity of intestinal fermentation. Aloysius Martin established that in every disease of the intestinal tube there was an increase of urinary indican. Hassal found a large proportion of it in the urine of people suffering from cholera; Gubler, in typhoid fever and cholera. One of Gubler's pupils—A. Robin—studied its variations in typhoid fever. Carter and

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[1] Phenol, according to Brieger, is excreted to the extent of 15 milligrams daily. This is a much smaller amount than is given by most authorities.—T. O.

Jaffe have shown that urinary indican increases in consequence of the retention of fæcal matter in intestinal obstruction and in internal strangulation. Senator showed the same fact in certain kinds of constipation; in these the alvine secretions are maintained in a liquid or semisolid state.

[There is considerable discrepancy of opinion as to the toxicity of indol, which, as already mentioned, is eliminated in the urine in the form of indican or indoxyl-potassium-sulphate to the extent of 12 milligrams in twenty-four hours. Jaffe (*Centralbl. f. d. Med. Wiss.*, 1872, No. 1), Nencki ("Ber. d. deutsch Chem. Gesellsch.," ix, 299), and Baumann (*Pflüger's Archiv*, xiii, 825, and "Ber. d. deutsch Chem. Gesellsch.," ix, 54) administered indol to dogs in their food, also by subcutaneous injection. Jaffe did not find that any poisonous symptoms followed the subcutaneous injection of indol, and it was not until Nencki had administered to a dog 2 grams by the mouth in twenty-four hours that there appeared diarrhœa. Frogs are susceptible to the influence of indol: 12 milligrams of a 1 per cent. solution when administered subcutaneously caused death. Rovighi (Maly's "Jahresb. ü. Thier-Chem.," xxvi, 456) found that from 1.5 to 2 grams of indol when administered subcutaneously to rabbits in twenty-four hours proved fatal, the symptoms being torpor, somnolence, general muscular weakness, feebleness of heart action, and a fall of temperature. Three healthy medical students agreed to take under Herter's observation (*New York Med. Jour.*, 1898, July 16 and 23) for a period of from six to thirteen days indol in varying quantities from 0.025 to 2 grams. In twenty-four hours on one occasion one of the students consumed 2 grams. He had taken on the first day of the experiment 1 gram without any ill effects. On gradually increasing the dose sleep became disturbed and headache was induced. Herter therefore does not attribute very highly toxic properties to indol. Beattie Nesbitt (*Journal of Experim. Med.*, vol. iv, No. 1, 1899) did not find that the injection of indol, 0.1 gram, into the jugular vein of a dog was followed by any marked change in the arterial pressure and therefore is of the opinion that to account for the symptoms in acute intestinal intoxication it is to the absorption of other substances we must look than to to indol.]

Analogous researches have been made for other substances by Salkowsky,—for phenol and cresol. We see them increase like indican in the urine, in certain forms of diarrhœa, and in intestinal obstruction. I will say the same of a substance, not defined chemically, revealed in the urine by a claret coloration induced by the addition of perchloride of iron to it. It has been observed by Senator, Riess, and Litten, not only in acetonæmia or sugary diabetes, in pernicious anæmia or leucocythæmia, but in grave dyspeptic states, in certain cases of carcinoma of the stomach,—all cases in which anomalous fermentation is produced in the digestive tube. I have also seen, often enough, this coloration of urine in the grave forms of dilatation of the stomach, in cancer of the stomach, and in typhoid fever. This material is assuredly not acetone; it is analogous to it only by this reaction when brought into contact with perchloride of iron. It was absent in certain diabetics whose breath, moreover, had the odor of acetone. I believe, with the authors named above, that it is frequently found related to increase of fermentation in the digestive canal.

All these substances, known or suspected, are only some of the products of intestinal putrefaction, but they show very well the parallelism between the entrance of putrid matter into the blood and its increase in the urine. We know, therefore, that if these putrid substances are formed in excess, there may result from them an intoxication even without the kidney being diseased. Nevertheless, as all these substances exist normally in the digestive canal, we may ask whether the organism has no other protection against them than the kidney. It is possible that the liver may give this protection, and that the experiments of Schiff relative to the alkaloids may be of a more general significance. This hypothesis may rest upon some experiments recently performed in my laboratory by G. H. Roger.

The alcoholic extract of rotten meat is twice less toxic when we inject it into the portal vein than when introduced into the general circulation. Extracts of the intestinal contents of the rabbit and the dog kill, by a smaller dose, frogs deprived of their liver, than healthy frogs, or those in which we have tied the afferent vessels of the kidneys. It appears, therefore, to be certain that the liver arrests or transforms toxic substances which originate in the intestinal canal. This conception again has been verified experimentally: blood drawn from the portal vein of the dog kills a rabbit in a dose of from 13 to 14 cubic centimeters per kilogram, whereas it is necessary to use 23 cubic centimeters of blood removed from the liver.

These recent experiments seem to lend support to a hypothesis put forward by Schiff a long time ago. You know that, in consequence of an abrupt ligature of the portal vein, the animal falls into a state of somnolence and dies in one or two hours, if it is a dog; in thirty or forty minutes, if the experiment has been performed upon a rabbit. Schiff supposes that the death is due to an intoxication consequent upon the retention of a poison which the liver was charged with the function of destroying. This poison would originate during disassimilation, and Schiff considers that he has demonstrated its existence by the following experiment: He removes the liver from a frog, the animal bearing the operation well; that is, without immediate death. He injects into it blood removed from a healthy dog; the frog does not die. He ties the portal vein of this dog, which falls into somnolence and dies. He takes some blood from this dog and injects it into the frog; this becomes, in its turn, somnolent, and dies, at the end of from half an hour to an hour.

The experiment has been repeated in my laboratory by M. Roger; he has injected into rabbits the blood of a dog, before and after ligature of the portal vein. In these two cases the toxicity has been the same, viz., 25 cubic centimeters per kilogram. This result—completely opposed to that of Schiff—does not cause me, in any way, to repudiate the idea that the liver arrests and is constantly transforming toxic products; the comparative toxicity of the portal and hepatic blood demonstrates it. Only, in the experiment of Schiff, poisoning has no time to be produced; the animal appears to succumb, as Claude Bernard has said, to an intestinal hyperæmia and consequent cerebral anæmia. In order to study auto-intoxication, after suppressing the function of the liver, it will be necessary to join together the portal vein and the renal. The experiment made by Holnikew, from another point of view, has allowed the animal to live from eight to ten hours.

I think that we may, therefore, conclude that the liver is an organ of protection to the economy; that it arrests more or less of the toxic material in general,—not the whole, since a part passes into the urine. The liver is certainly not the only agent which acts the part of protector to the organism against poisons. There may yet be made to intervene, as an auxiliary agent of protection, rapidity of intestinal expulsion by the stools,—hardening of the intestinal contents, which, transformed into a hard, fæcal bolus, becomes almost inoffensive, because it no longer allows of absorption. [Medical men are familiar with the readiness with which convulsions are induced in infants as the result of imperfectly digested food passing down the intestine. Hepatic insufficiency, either by not arresting or not transforming toxins elaborated within the alimentary canal is also a cause of convulsions in young children and in adults.]

After having admitted this hypothetical and theoretical mechanism of intoxication by poisons of intestinal origin, let us see if there exist, really and clinically, such intoxications. On this point I shall borrow from the teaching laid down in the work of M. Humbert, who has used the word intestinal septicæmia in the sense of intoxication. I find therein startling examples of intoxication in some of the phenomena which are produced in the course of surgical affections causing intestinal obstruction. In the first place, mechanical phenomena are demonstrated by the arrest of matter, pain complained of above the obstacle, and abdominal distension. Then reflex actions: vomiting which cannot be attributed to intoxication, fall of arterial tension, frequency of the pulse, perspiration, etc. All these reflexes are often arrested at the end of one or two days, and during these two days vomiting ceases. Then appears a new phase, characterized by prostration and collapse,—a particular pallor of the skin, not pale, owing to spasm of vessels, but earthy-looking, from being impregnated with coloring matter; coldness, and muscular cramps. Humbert asks whether a part of this complicated clinical picture should not be attributed to intoxication. We must certainly reply to him in the affirmative. Why this period of respite? It is inexplicable on the theory of reflexes. It finds, on the contrary, an explanation in intoxication. Examination of the aforementioned facts does not offer to us, doubtless, a true demonstration, but it forces us to reconsider the question. It is not uncommon to observe cases of strangulated hernia in which accidents continue when the intestinal strangulation has been relieved, because putrid material is freely spread throughout the whole length of the digestive tube, which absorbs it.

An objection often made to the hypothesis of intoxication of fæcal origin is the fact that constipation is compatible with health. If this hypothesis were true, say some, intoxication would be realized to the full in constipated people. I reply that constipation ought to be regarded as a protection against intoxication. It supposes that all that is absorbable has been absorbed,—the aqueous part with what was held in solution. In constipation there is, at first, a preliminary phase, in which appears a threatening of intoxication, but, in the second place, intoxication is no longer in operation.

Besides, are constipated people healthy? They have headache, migraine, and vertigo. Hypochondriacs, whose sufferings are chiefly subjective, are constipated. They experience a number of nervous disorders of sensibility,—buzzing in the ears and psychical troubles. All the insane are constipated, and alienists endeavor specially to guard against constipation. I do not say, of course, that psychical troubles are caused by constipation. I only say that they are, in a certain sense, exaggerated by it. I say that the nervous system is maintained in a condition of hurtful disposition by constipation, and that we render a service to patients attacked by cerebral trouble when we cause to disappear, at the same time as constipation, the unhealthy disposition of the nervous system.

Thus we see, in the two examples of septicæmia of Humbert, and of constipation, the maximum and the minimum of accidents attributable to the intoxication of intestinal origin.

[Bouchard himself partly answers the question raised higher up: "Are constipated people healthy?" A short while ago I published notes of a case where the bowels had not been opened for nearly forty days. In this woman, very shortly, almost immediately, after the constipation was relieved her mental symptoms disappeared and her temper and disposition improved. Constipation favors auto-intoxication by allowing absorption to take place, and while it is true that, owing to the hardness of the stools the poisons included therein do not readily escape, still not only are there experienced by the patient headache, migraine, and vertigo, but, as shown by Vanni ("Sull' origine intestinale della Chlorosi," *Il Morgagni,* p. 533, 1893), the red blood-corpuscles become diminished in number and less resistant to the action of destructive agents. Persons engaged in the ordinary duties of life and who are daily taking exercise may not for a time complain of symptoms due to constipation, but some illness arrives, an accident occurs requiring surgical operation, or a woman is confined, then constipation, until then apparently harmless, becomes a cause of feverishness and restlessness. It is good practice on the part of surgeons to prepare their patients beforehand for abdominal and other operations by inducing intestinal antisepsis by means of aperients.]

# LECTURE XVII.

## ACUTE OR TRANSITORY INTESTINAL AUTO-INTOXICATION—GASTRIC DISORDERS—INDIGESTION—POISONING BY TAINTED MEATS.

**Explanation of the symptoms of gastric disorder from retention of toxic material in the stomach. Washing out of the stomach in certain forms of intestinal obstruction. Indications for emptying the intestines in surgery and obstetrics.——Indigestion, with excessive production of toxic matter in the digestive canal. Presence of sulphuric acid in the intestines and emunctories in a case of grave indigestion (Senator). Case of indigestion with enormous quantity of alkaloids in the intestines and urine.——Poisoning by tainted meats: old sausages. The epidemic at Andelfingen. Why these morbid states are intoxications and not infections.**

I HAVE just shown you, in internal strangulation and in constipation, the two extremes,—the maximum and the minimum of intoxication of intestinal origin. In the morbid state—still badly known—which we call *acute dyspepsia,* things are, at their origin, obscure and complex. We do not know what is the primary cause of gastric fullness, but we do know that there exists in this affection, at a given moment, a diminution of the secretions; of the saliva, whence the clammy state of the mouth; of the gastric juice, whose peptogenic power is weakened; of the intestinal glands, which causes constipation. The appetite is diminished, and that is very advantageous, since the digestive power is less, and also because the taking of food in as large a quantity as under ordinary conditions would transfer to parasitic ferments more putrescible material. In these conditions of imperfect digestive secretions I see the possibility of a development of anomalous fermentations. It is certain that the subjective troubles felt by patients cannot be explained by an insufficient alimentation of so short a duration. On the contrary, the production of putrid fermentations explains the bitterness felt in the mouth, headache, and depression. If I have not, therefore, any information as to the primary cause of the disease, I have reasons for supposing that one part ought to be attributed to intoxication in the pathogenesis of some of the accidents.

In certain individuals habitually the subjects of diarrhœa, who have, nevertheless, during each day, only one liquid and fetid stool, we observe nearly always headache, vertigo, and some shivering. In general, they experience bitterness in the mouth; their breath and their skin have a disagreeable odor. But all these inconveniences may disappear for a time by evacuating the contents of the large intestine. The individual who awakens with a sensation of lassitude may be deprived of it by a simple injection. What I say to you in regard to this does not constitute a demonstration, but it is more a reason for adding to the probabilities in favor of the part played by intoxication in the genesis of troublesome, though attenuated, nervous symptoms, apart from any completely established disease.

We may see more severe symptoms yield after simple evacuation of the contents of the digestive canal. Washing out of the stomach is not a curative means, properly speaking; but it removes certain forms of malaise, headache, and migraine. In certain patients, the subjects of dilatation of the stomach, lavage causes not only the disappearance of pain, pyrosis, and heartburn, but all the other accidents called reflex. Assuredly washing out does not cure dilatation of the stomach, but it is in certain cases necessary, and it renders considerable service in weakening the most painful symptoms,—services which are manifest, but, unfortunately, also transitory. In my clinique was a woman whose stomach was dilated. She suffered from constant supraorbital headache. Washing out was always immediately followed by a disappearance of this headache.

When the stomach retains substances more toxic, which happens, for example, in intestinal obstruction, washing out has a utility no less observable. Senator had formulated this indication. M. Chantemesse was able to verify the reality of this in a patient, in my service, attacked with an intestinal obstruction from an unknown cause. Fæcal vomiting bore witness to the accumulation of toxic material in the stomach, and would explain the general symptoms which accompany intestinal obstruction: the small pulse, coldness, owing to paralysis of the cutaneous vessels, etc. Four liters of a horribly fetid liquid were evacuated by means of the œsophageal tube, and we saw the disappearance of symptoms of peritonism, which so closely resemble intoxication. A new accumulation of fæcal matter was followed by a return of the grave symptoms, which evacuation of the contents of the stomach again caused to disappear and cured the individual. He was cured not by lavage, but thanks to the lavage, which gave him respite by arresting intoxication and in giving to him, I presume, time for the strangulation to free itself. There are, therefore, cases in which toxic accidents caused by the reflex of putrid material into the stomach have disappeared, thanks to lavage.

There are other circumstances in which we might suppose that stagnation of intestinal material causes fever. After laparotomy the fever cannot be explained, in many of the cases, by a septic condition of the peritoneum, and we see it disappear after getting rid of constipation (Küstner). Accoucheurs know quite well how certain febrile incidents which supervene in the course of parturition disappear after alvine evacuation, either spontaneously or induced by light purgatives. This hurtful influence of the stagnation of matter in the intestines after operations explains old traditions forgotten in surgical practice. It was the rule in olden times to prepare those about to be operated upon by administering to them in succession an emetic one day, then on the following day a purgative, and that in two or three takings. We no longer push to the same extent to-day this preventive line of therapeutics; but, the operation concluded, unless it be one upon the abdomen, we can, with advantage, it would appear, and upon the evidence of M. Verneuil, induce intestinal evacuation. These, then, are clinical facts which agree with theory.

There are cases in which we have been able to demonstrate that the grave accidents of a true indigestion were of a toxic order. Senator has seen in one of his friends a fact of this kind,—in whom intoxication resulted from sulphuretted hydrogen produced in the intestines of the patient. There had been vomiting and eructations, giving off, as well as the gases emitted by the anus, the odor of rotten eggs. The symptoms consisted of fainting, anxiety, and clouding of the intellect. But the poison could be detected in the emunctories; the emitted gases blackened paper impregnated with acetate of lead; the stools and the urine contained sulphuretted hydrogen. We could therefore notice in these cases certain symptoms which contribute in part to the classical picture of poisoning by $H_2S$, as in certain dyspepsias. We have demonstrated the presence of this poison in the intestines, and then in the urine; it is therefore certain that it had traversed the blood.

[Sulphuretted hydrogen gas is normally produced in small amounts in the intestine. When thrown off in the urine it constitutes the condition known as hydrothionuria. By some physicians and physiologists the nervous phenomena observed in Senator's case of hydrothionuria are not attributed to the circulation of sulphuretted hydrogen in the blood. Herter, for example, considers the question as unsettled. As to the toxicity of the gas there is little doubt, for experiments and experience alike confirm the fact. It is largely a question of the amount. To the production of this gas in the intestine putrefaction or fermentation contributes in no small degree. Many aërobic and most of the anaërobic bacteria can, when the hydrochloric acid of the gastric juice is deficient and oxygen is absent, bring about a disintegration of proteid during which sulphuretted hydrogen is given off.]

In some people special foods, without being either toxic or putrid, induce regularly an indigestion and grave phenomena. In similar cases, if there is intoxication, it is the result, not of the food, but of the nondigestion; the digestive juices cease to transform food which the stomach does not care to receive; the nervous system produces disorders of secretion; the gastric juice stops flowing into the stomach, or else the HCl is absent from it at the moment of the conflict of the food with the microbes. But the HCl not only serves the purpose of swelling and of hydrating the alimentary mass, it ought to protect it against parasitic ferments. These being no longer neutralized, anomalous fermentations are produced in the stomach and in the intestines; the toxic products of these fermentations are reabsorbed. There arises from this an intoxication, which is not serious, fortunately, because the renal function protects the organism.

In 1882 I made known the following observation: A man could not take fish, cooked the day before and eaten cold. One day, when he had partaken of this, which his nervous system did not accept, digestion was arrested, and he experienced the ordinary symptoms of an indigestion, at first stomachal and then intestinal. Diarrhœa lasted not only until the last particles of the ingested food were eliminated, but well beyond that even. It was accompanied by prostration and anguish. But the first accidents only appeared after a veritable incubation of eight hours, during which, without doubt, microbes had formed the amount of poison which caused so prolonged an intoxication; and, in order that there should be formed such an abundance of the poison, it was necessary that there should have been an undoubted multiplication of normal bacteria in the digestive canal. In fact, I have been able to estimate the quantity of microbes, in these cases, as one-third of the fæcal mass. There was an increase of the intestinal alkaloids, since from 12 grams of fæcal matter I was able to remove sufficient alkaloids to estimate the proportion of it as 15 milligrams per kilogram of fæcal matter. In the urine was also found a quantity of alkaloids fifty times greater than the normal amount.

That is a case, therefore, in which, without there having been an introduction of meat in a state of fermentation into the digestive canal, and without our being able to establish particular microbes, there was produced, by the multiplication alone of normal bacteria, a considerable increase of one, at least, of the toxic substances which the intestine ordinarily receives. I know of the circumstance of three people who were simultaneously seized by accidents of the same kind. Breakfasting together, they had eaten fish, with a certain distaste, about 10 or 11 in the forenoon. At 7 o'clock at night one of the three felt indisposed; the other two sat down at table, but found themselves attacked, at the time of dessert, by identical symptoms. It was a question of an illness consisting of vertigo, prostration, vomiting, and diarrhœa. These symptoms were not the result of an intoxication, since they only appeared after an incubation of eight hours. The diarrhœa was not that which supervenes in indigestion and which ceases immediately after the elimination of food not digested; it continued, night and day, during eight days, with from eight to fifteen evacuations daily. The patients remained, all this time, in a semi-sleepy condition. The three people are now cured, and for all of them the duration of the illness was the same. This disease might be attributed, quite legitimately, to a putrefaction which had taken place in the digestive canal, and to a reproduction of putrid agents which had formed poisons.

We must recognize in these facts something analogous to poisoning by sausages, known for a century and a half,—since 1735. Facts are plentiful. Muller, in 1869, had collected 263 observations. Some have sought for the toxic material in the residue of meat. This research had remained, without any result, until Hoppe-Seyler discovered the existence of an alkaloid, but without demonstrating its toxicity. Brouardel and Botmy, more fortunate, have demonstrated the toxicity of an alkaloid which was contained both in the viscera of a woman who died, after having eaten some preserved goose, and in what was left of this goose. This alkaloid presented analogies with conicine, but also differences.

It is certain that true intoxication may result from the eating of tainted meats. Gaspard and Panum have shown that the putrefaction of meat develops a poison capable of inducing accidents both serious and fatal. But in these cases the symptoms are quickly developed; they commence half an hour after the ingestion of tainted meat. Besides, in a general way, we do not eat meat actually putrefied and already capable of intoxicating by itself. We ingest meat which is only beginning to putrefy, in the depths of which microbes are at work determining a fermentative process, which goes on, under conditions particularly favorable, when the tainted food has found its way into the digestive tube. The accidents which result from it are slowly developed; they only light up from eight to eighteen hours after the ingestion of suspected foods. In this period of incubation no symptom reveals the explosion which is preparing; but, once the poison is formed, toxic accidents are quickly developed.

Krautzer has related a case of intoxication by sausages. Four people had treated themselves to Wurtemberg sausages scarcely sufficiently cooked, for people with delicate tastes prefer particularly sausages the superficial part of which alone has been influenced by the fire. Out of these four people, one remained free from any symptom, the other three were taken ill, and one of them died. After an incubation period of eighteen hours, the symptoms experienced were almost identical in intensity; they consisted in disturbances of sight—strabismus, diplopia, ptosis, pupillary dilatation—and paralytic phenomena. Injections of pilocarpine which were made did not induce perspiration. Thus, there is a form of intoxication caused by a poison which dilates the pupil and hinders the secretion of sweat, which, consequently, is not without analogy to atropine. And yet, among the putrid alkaloids, there is one, endowed with analogous properties, which I had formerly extracted from the fæcal matter of patients the subjects of typhoid fever,—a disease in the course of which intestinal putrefactions are very intense.

We have just witnessed a small epidemic in a family. We have also seen epidemics of a similar nature visit with severity a whole locality. The unwholesome flesh of an animal is given out for consumption in a village, at the time of a *fête,* which draws a great many people there. The incubation of accidents having been long among the first consumers, the tainted meat continues to be distributed among the people who have come from neighboring villages. These, returned each to his own house, are seized with identical troubles, and quite a series of small epidemics is developed, having for its origin the infection caused by the unwholesome meat consumed in the village where the *fête* had taken place.

Twelve years ago I broke the lance with Lebert in the interpretation of the epidemic at Andelfingen. In the little town in Switzerland a large number of deaths resulted from an intoxication due to diseased meat. And yet there was always a slow incubation and a long duration, which eliminated the idea of intoxication. There was question rather of a disease which developed gradually in the individual, and continued after the complete elimination of the tainted food. In similar cases the substances—although wholesome—after ingestion putrefied in their turn.

Some have thought that this disease was trichinosis or typhoid fever. Griesinger was party to this last opinion. Lebert, on the contrary, was inclined to regard it as an intoxication from tainted meat. Having had the documents in hand, I insist upon the long duration of the incubation which was observed in the patients. It has been shown since that there could not be any question of trichinosis. At the autopsy of some of the people who had been at that time ill, and had recovered, made a long time afterward, no calcified cysts were found in their muscles. If one allies himself with the opinion of Lebert, he can only accept the unwholesome meat as having caused the intoxications; the accidents can only be explained by the mechanism of infection. Why had certain individuals no sign of illness, in spite of the fact that they consumed the same meat as those who became ill or died? It is probable that they had eaten the parts of the tainted meat that were the best cooked,—the external parts,—where the action of heat had in part neutralized the poison.

Thus, in the family epidemic of which I have just spoken, out of four people who ate the same sausage, one remained free from accident. This fortunate individual was the apprentice, and to whom the masters had given the crust of the sausage,—a part much less prized by them than the central, but in which microbes must have been destroyed by the action of heat. The infection in the cases which I have just examined is not an infection without any relation to intoxication, for there is no question of a general infection, but of a surface infection. Without doubt, there is at once induced an increase, more or less rapid and enormous, of the quantity of infectious agents introduced into the digestive canal; but, secondarily to infection, there is, in all probability, produced an intoxication. There are infectious maladies in which microbes inhabit the blood; they can subtract oxygen from the blood-cells or from emboli in the small vessels. There are other infectious diseases where microbes are present in certain tissues and induce therein anatomical lesions. In all these cases the symptoms and deaths are easily explained. But there are other infectious diseases where microbes only exist upon a mucous surface, where they do not penetrate, and do not alter the limiting membrane. How, in these cases of surface infection, are we to explain the general symptoms and death, if it be not by intoxication? The danger as regards the organism can only arise from the absorption by it of the toxic products secreted by the infectious agents. The small microbes form poisons like many large mushrooms.

There are cases in which infection no longer operates in an acute transitory manner, but during several months and years; it is the result of habitual putrefactions, of which the digestive tube is the seat, in many of the chronic diseases which affect it, and which are opposed alike to good digestion as to the healthy elaboration of material. This is seen in cancer of the stomach, in certain chronic dyspepsias, and in dilatation of the stomach. Thus, besides the inconveniences which, from a nutritive point of view, flow from imperfect digestion and insufficient alimentation, we see symptoms and alterations arise which bear witness to the chronic deterioration of the organism by intoxication.

# LECTURE XVIII.

## CHRONIC GASTRO-INTESTINAL AUTO-INTOXICATIONS—DILATATION OF THE STOMACH.

Chronic auto-intoxication, having as the point of its origin the digestive canal, is observed in chronic diarrhœa, cancer of the stomach or of the intestine, and in chronic dyspepsia. Dilatation of the stomach may be taken as the type of the morbid states which produce chronic auto-intoxication.——Incredulity of a part of the medical public as regards the subject of dilatation of the stomach. Its frequency demonstrated by clinical statistics. Why it has been until now unknown. It can only be revealed by physical signs. Insufficiency of percussion as the means of diagnosis of dilatation. Value of the splashing sound as a means of delimitation of the stomach.——Consequences of gastric dilatation.——Direct symptoms on the side of the gastric tube and its annexes. Gastritis. Gastro-intestinal dyspepsia. Hepatic congestion. Ectopia of the right kidney: floating or mobile kidney only exists in women and military men; it is induced by repeated congestion of the liver in people the base of whose chest is made to undergo habitual constriction.——Accidents remote and at a distance. Disorders of innervation: sensibility to cold. Disorders of the senses and intelligence. Disorders of general nutrition and of the emunctories. Skin affections. Catarrh of mucous membranes. Albuminuria and peptonuria. Inflammation of certain tissues and of phlebitis.——Alterations of the osseous tissues: deformity of the phalango-phalangeal articulations of the fingers. Its semeiological value; possible relation between dilation of the stomach, rachitis, and osteomalacia.——How can we explain the reaction of dilatation of the stomach upon the whole of the organism? Beau had already taught how dyspepsias produce an impression upon the nervous system. Dyspeptic coma.——General accidents of dilatation of the stomach are no more surprising than those of nephritis. Functional dignity and importance of the digestive canal in the relative positions of the organs. Why the train of symptoms in dilatation of the stomach should not be confounded with arthritism; it constitutes, at the most, *minor arthritis.*——Clinical types of dilatation of the stomach: latent forms, dyspeptic, hepatic, neurotic, cardiac, asthmatic, renal, cutaneous, rheumatic, acute or chronic consumptive.——Diseases of debility in which dilatation of the stomach is induced: chlorosis, tuberculosis.——Dilatation of the stomach is the result of an acquired diathesis.——Gastrictetany: Bouveret-Devic, Halleburton-McKendrick.

THE facts enumerated in the preceding lecture do not all constitute a strict demonstration of intoxication,—they only cause it to be presumed. Nevertheless, there are some of them which carry conviction,—that of Senator, for example, in which one poison only—sulphuretted hydrogen—was found in the intestine and in all excreted products: that which is personal to me, and in which I have found alkaloids in enormous quantity in the urine, as well as in the intestine.

Secondary intoxication can alone explain the fatal accidents consecutive to surface infection; for, if we understand the mechanism of death in diseases where the infectious agent is spread out in the whole of the organism, in the blood, or in the principal viscera, how could life be arrested by a disease in which the infectious agent rests on the surface of the mucous membrane of the digestive tube, if that infectious agent does not form a poison which, being absorbed, diffuses itself through the whole economy so as to impregnate the cellular elements or to energetically impress the nervous system?

There are, besides, cases in which some have been able to isolate and define chemically toxic bodies; Brouardel and Boutmy have done so. There are others where the symptoms observed bear a remarkable analogy to certain well-known forms of poisoning. Lépine and Daniel Mollière saw a case of intestinal obstruction followed by accidents simulating intoxication by atropine, with scarlatinal redness, mydriasis, and acceleration of the pulse.

We are now going to approach chronic intoxications having as their point of origin the intestinal canal. They may be observed in chronic diarrhœa, in cancer of the stomach or intestine, in chronic dyspepsia, and, above all, in dilatation of the stomach.

A year ago I brought forward the statistical analysis of 220 cases of dilatation of the stomach which I had personally observed. I could bring forward to-day nearly 400 cases, of which 274 have been seen by me outside of the hospital, and the others in my service. When I announced to you, last year, my views upon the consequences of dilatation of the stomach, I had not met opponents by word alone. But at the Medical Society of the Hospitals, in the press, and in conversations with *confrères,* I have found incredulity and jesting, which in our country always welcome a new announcement. I believe that my opponents have passed beyond the question; that they cannot judge otherwise, because they were in want of facts to control my way of viewing it. I do not know whether my opponents have subsequently made the control of that which I had advanced;

but I have done it. Some may say, it is true, that my control ought to be held only as a suspicion. And yet, if I am not mistaken, it seems to me that the denials, which were universal, are fewer and less noisy; they may carry with them divergence of opinion as to the frequency of such a fatal concomitant, or of the disease itself, but people no longer deny the existence of it.

I have said that dilatation of the stomach was neither an anatomical curiosity nor a rarity; that, while very frequent in the sick, it is relatively uncommon in the healthy; and I have myself asked the question whether people who, in appearance, are not ill, but still have the physical signs of dilatation of the stomach, are truly healthy? I have said that, generally speaking, gastric dilatation had existed for a long time before the commencement of the disease with which we find it associated, and that there is a cause for considering, in a very large number of patients, besides the principal disease by which they are designated, the other, dilatation of the stomach, which has the appearance of being an accessory, and which has, perhaps, prepared the way for invasion of the first.

Why has dilatation of the stomach been so little known for such a long time past, and yet so frequent? Because it cannot be recognized save by establishing its physical signs; but oftenest, on examination of the patient, the symptoms of which they complain are not of the nature to lead us to search for it.

Indeed, I can affirm, from an analysis of the facts, that dilatation of the stomach may exist without inducing anomalous sensations, without dyspeptic or gastralgic symptoms, in two-thirds of the cases. It is a disease which does not announce itself; we know that it passes unperceived.

The physical signs which permit of the recognition of dilatation of the stomach can be furnished by different methods of clinical examination. Percussion is difficult and delicate to practice, sometimes insufficient, and is rendered false in its results, owing to tympanites of the colon. Succussion furnishes no certain sign; it may bring out the noise of fluid in a normal stomach, and yet it cannot reveal the extent of the dilatation.

I have pointed out as the best sign the sound of splashing, already drawn attention to by Chomel. But it is necessary, in order that it should have the whole of its semeiotic value, that there should not have been recently the ingestion of any considerable quantity of food capable of producing mechanically a fleeting distension; it is necessary that splashing should be detected in a person who is fasting. If you do not hear it at the first stroke, you must not affirm that the stomach is not dilated. It may be flattened and fall flabbily behind the abdominal wall, like an apron; but if you introduce one-third of a glass of water into a dilated stomach, you will immediately hear splashing over a region much greater in extent than in the normal state. In the healthy man this phenomenon is never perceptible fifteen hours after a meal. I still admit, through courtesy, that it is necessary to perceive the splashing below the middle of a line drawn from the umbilicus to the point nearest to the border of the left costal arch. But, in reality, this line is of little importance. Every stomach which is not retracted when it is empty is a dilated stomach. Dilatation is not distension. A dilated stomach is a stretched stomach the cavity of which is apparent only when it is empty, because, though its walls then touch each other, it is no longer capable of diminishing its own size by retraction.

It is not enough to know only that the stomach is dilated; it is necessary to know, in a precise manner, the dimensions of this dilated stomach, to know its extreme limit below and its extreme limit to the right of the median line, to pursue the search after splashing until it disappears from above downward and from left to right, and to establish thus its limits by the determination of the two lines, traced upon the limits of the zone where we observe splashing,—one of these lines being horizontal, the other vertical, parallel to the median line and situated to the right of this line.

Is it possible, as some have said, to confound stomachal with intestinal splashing? No; this is heard lower down. Besides, we proceed to seek it from above downward, and from left to right. In addition, it is easy to establish that the arrival of water in the stomach is immediately followed by the noise *(bruit)* of splashing; water has not had sufficient time to reach the colon. I still insist upon the necessity of assuring one's self of the constancy of the phenomenon, which, sought for under the same conditions, ought always to be perceived at the same points.

If the demonstration can be considered as clinically accomplished, it is also anatomically. We can cause chopping to appear in the cadaver, and we delimit the dimensions of the area where it is heard; we open the abdominal wall, and we can convince ourselves that these are indeed the limits of the stomach; afterward, we sew up the wall, and anew we observe chopping within the same limits.

Be certain that we do not often give ourselves the trouble of seeking for dilatation of the stomach in the exact conditions which I have indicated, and still less of measuring it. Yet we ought to be able to know exactly the number of centimeters which a stomach measures. If there truly exist marked dilatation of the stomach, such as I have indicated; if there are stomachs which, during several years, reach almost to the pubis, as we have been able to verify them at the autopsy, it appears *a priori* impossible that such an anomaly could exist without disturbance of health. Assuredly, one can have a large stomach and not experience dyspeptic troubles, but he is the victim of disturbances in the elaboration of food. Men whose stomachs are dilated complain of their indisposition as being of very slow development; they are, nevertheless, ill for a long time before becoming patients. Their diseases are, therefore, diseases of debility, because the alimentary material, incompletely digested and undergoing putrid fermentation, is no longer sufficient for their nutrition. They are victims of an insufficient alimentation both because the imperfection of digestion reduces the value of assimilable material and because putrid fermentation destroys another part of this, for the hydrochloric acid of the gastric juice, being too diluted, is no longer capable of offering opposition to the anomalous fermentative actions induced by the figured ferments.

We notice, then, in individuals who present the physical signs of dilatation of the stomach: 1. Pulmonary phthisis. 2. Chlorosis (both of which accompany gastric dilatation,—the first in two-thirds of the cases, the second in four-fifths). 3. Nervous or hypochondriac symptoms. We see men without energy, who present themselves at the hospital because they can no longer work, on account of physical and mental debility; we regard them often as idlers, if not as hypochondriacs; we make an error in diagnosis. 4. Last, other symptoms, so varied and so numerous that their mention at first provokes general incredulity.

I shall not return to the details which I gave last year upon this subject. I ought, nevertheless, to make again a brief mention of them. We meet, among patients whose stomach is dilated, *symptoms directly connected with the digestive tube.* The appetite is in general preserved; it may be augmented. The most of those who are the subjects of dilatation eat largely. Ingestion is not at all painful. But, at the end of two, three, or four hours, the stomach is blown out, eructations are produced, inodorous at first, then musty, sometimes fetid; a sensation of heaviness or of heat at the epigastrium; pyrosis; regurgitations, whose acid odor demonstrates the reality of the anomalous fermentations which are going on in the stomach, for the hydrochloric acid has no acid odor. This is due to acetic acid. The fæces are generally doughy, stinking, acid; although soft, they are expelled slowly, and with pain. Their acidity is due, we can assure ourselves, to the predominance of acetic acid.

The consequence of this development of acid in the whole length of the digestive tube is an inflammatory condition. We notice catarrh of the stomach, ulcerative gastritis, to which patients often succumb after twenty-five years of *bad stomach;* these are the *false cancers,* as they are called, or malignant gastritis without tumor. The large intestine is inflamed; around the fæcal matter are seen glairy secretions and sometimes blood (membranous enteritis).

Besides the phenomena of gastro-intestinal dyspepsia, there exists hepatic congestion. We find in people with dilated stomach, a swollen liver, often indolent; sometimes there exists an aching in the right hypochondrium; sometimes jaundice without colorless stools. This congestion of the liver is of short duration, and is modified very rapidly; it may appear and disappear in two or three days; it sometimes, too, passes unnoticed. Of the 274 cases which I have observed outside the hospital, I have found it 13 times in 100; that is to say, in one-eighth of the cases.

The knowledge of this tendency to hepatic congestion is not without interest, from the point of view of the explanation of the recurring jaundice of infants. It also explains, perhaps, the ectopia of the right kidney, which I have always seen coincide with a dilatation of the stomach, but I can only believe that this coincidence is accidental. It was made, in 1875, by Bartels. This observer has an opinion different from mine as to the bond which unites these two facts,—ectopia of the kidney and dilatation of the stomach. Bartels believes in the primary displacement of the kidney. The kidney, says he, falls upon the horizontal portal portion of the duodenum and opposes mechanically the departure of food from the stomach, which thus dilates. But if the kidney is displaced primarily, why is it always the right kidney? I say that the right kidney is dislocated, because it is the liver which pushes it out of its place. We do not find ectopia of the right kidney in all people whose stomach is dilated, but only in those whose thorax is the seat of an habitual constriction at its base, in women and military men. Bartels has recognized this fact. The corset and the abdominal band prevent the liver, when it increases in volume, from passing in front of the kidney. Thus, if, ten or fifteen times a year, there are produced sudden developments of hepatic congestion, we can easily understand how the kidney, pressed against, little by little, is displaced consecutively to the gradual elongation of its vascular attachments. We observe, in all the cases of dilatation of the stomach, luxation of the kidney 14 times out of 100. If we consider sex, the frequency is 28 per cent. in women and 3 per cent. only in men. Thus, if in women more than one-fourth of the dilatations are attributable to luxation of the kidney, dilatation of the stomach ought to be in men sensibly less frequent than in women. Yet experience shows that dilatation of the stomach is at least as frequent in men as in women.

Dilatation of the stomach, on account of the anomalous fermentations which are the consequence of it, is accompanied, besides, by *distant disturbance,* many of which form part of the classical series of dyspepsias and are considered to be reflex.

These are first the *nervous symptoms* of dyspeptics (dyspepsia is accompanied by dilatation of the stomach in seven-eighths of the cases).

Those who are ill are depressed in the morning, on awakening; at the end of half an hour they have often recovered their alacrity. They complain of a painful circle round their head, of headache, of feeling very depressed, an uneasy feeling generally; sensibility to cold, insomnia, vertigo, which belong to the history of all diseases of the stomach; obscuration of sight, hemiopia, diplopia, weakness of the right internal muscle of the eye, hallucinations of sight; partial and fleeting dropsy of the limbs,—of an arm or a leg; contracture of the extremities of the hands, as pointed out by Küssmaul, Dujardin-Beaumetz, Hanot, and Hayem, and of which I have recently met with an example. I have seen a patient who, at 2 o'clock in the morning, awoke in a start, and in a state of grief, with a contracture of the hands,—a contracture which extended up to the arms and the shoulders; this condition lasted for five weeks. I detected in her a dilatation of the stomach, and prescribed the appropriate treatment; on the following night she had not the crisis, nor had she it on the subsequent evenings, so long as she observed the regimen. One day she failed to do so; the same evening contracture of the hands reappeared. It has entirely disappeared since, thanks to the continued observance of a better hygiene.

I have noticed, too, transitory aphasia, and once fatal syncope, disturbances of vascular innervation, a sensation as if two or three fingers were dead, palpitation, flushing of the face two or three hours after meals, false angina of the breast, nocturnal perspirations (limited to the head, neck, and thorax). I would also mention, following Chantemesse and le Noir, bilateral intercostal neuralgia.

All these phenomena may be, strictly speaking, regarded as reflex. But there are others which arise from the abnormal metamorphosis of matter. And, as for these, how are they to be explained if not by intoxication?

Besides the nervous symptoms which are rightly or wrongly considered reflex, I have detected, in people whose stomach is dilated, *symptoms on the side of the general nutrition* and *disturbance of the emunctories.*

I have said that they are, in general, patients who are chilly; they have, nevertheless, free perspirations, night and day, and after the least exercise,—a walk on foot upon even ground, or after having ascended two flights of stairs. These perspirations have a heavy or musty odor, as of moldy bread, according to the statement of some of the patients.

We notice among them eczema thirteen times out of one hundred, pityriasis in front of the sternum or of the head, pityriasis versicolor.

Urticaria is not uncommon among those suffering from dilatation. But urticaria, although it does not pass for a disease of intoxication, and although it is not frequently noticed in the course of infectious diseases, yet it has arisen, in some unexplained way, during indigestion and gastric embarrassment. We have seen it follow the ingestion of mussels, certain stale fish, and various shellfish. Are not all of these toxic causes? Urticaria has often been observed after puncture of hydatid cyst of the liver; it has been attributed, in similar cases, to the introduction of a part of the fluid of the cyst into the peritoneum and to its subsequent entrance into the lymphatic channels; it would be, even there, a kind of intoxication. It is not correct that some should put as the cause of it exclusively the action of the peritoneum. While *chef de clinique,* I have seen a young girl, the subject of an hydatid cyst, upon whom Behier had advised a large opening of the liver to be made by means of successive cauterizations, after the manner of Récamier; in order to bring about adhesion with the abdominal wall, he had, by means of Canquoin paste, produced a kind of tunnel into the hepatic tissue. He reached a cyst of a size so small that he thought there were multiple cysts and that he would have to resort to puncture, to be made in the depths of the tunnel. There only flowed out a few spoonfuls of a liquid clearly hydatid, in which hooklets were detected by the microscope. He pushes the treatment further, and there is seen to escape a jet of red blood from a branch of the portal vein. And yet the only accident after this was a general eruption of urticaria. It is evident that penetration of the liquid of the cyst took place directly into the blood, and that there was here clearly a case of toxic urticaria without any intermeddling of the peritoneum.

Besides, I think that urticaria is often of a toxic nature, like other congestive eruptions with vesicles on the skin; quinine eruptions, which may assume the erythematous form; scarlatinal or papular, like a variety of the erythema due to copaiva, or like the exanthem of belladonna.

In certain young girls we see acne on the temples—on the parts about the chin—coincide frequently with dilatation of the stomach, as well as acne rosacea, with scarlet redness of the nose and cheeks, which develop about two hours after meals, and which, for a long time past, have been considered as indications of a bad stomach. Are not these cutaneous manifestations of toxic origin, like those which often follow the ingestion of chloral?

I suppose that, as the result of the ingestion of these various medicaments, the cutaneous vasomotors are impressed by the direct action of the poison, or their disturbance is the result of a reflex of the nervous system. Yet, when it is a question of morbid secretions, like acne and eczema, it is difficult to admit the interference of the nervous system. Would it not be more advisable to incriminate the elimination of fatty volatile acids? Whatever may otherwise be the interpretation, the empirical fact of the linking on of dilatation of the stomach to a large number of cutaneous manifestations remains certain; it is therefore, a series of links, and not an accidental association. For a pathogenic explanation I propose to you, for the time being, intoxication.

The mucous membranes, like the cutaneous coverings, serve for the elimination of gaseous matters and volatile fatty acids arising from abnormal fermentation which has taken place in the stomach. The odor of the breath is a witness to their elimination by the respiratory mucous membrane. Besides, people who are the subjects of dilatation of the stomach catch cold easily, cough habitually; their bronchi secrete mucous sputa which are with difficulty detached, and lead up to dyspnœa and rhonchi. I have found sibilant, noisy, recurrent bronchitis ten times in every one hundred of my actual statistics (instead of 15 per cent. in my statistics of last year); dyspnœic respiration of paroxysmal character, recalling the advent of asthma, four or five times in every one hundred. I have also noticed recurring coryza and frequent sneezing in the morning. These, also, I suspect, we must rather consider the result of the elimination of toxic substances than a reflex act.

[Discussing the various causes of asthma Dr. James Adam ("Glasgow Hospital Reports," p. 171, 1900) draws attention to the possibility of some forms of asthma that exhibit periodicity being toxæmic. Some patients who are afflicted with asthma suffer from catarrh of the respiratory mucous membrane or something akin to an internal urticaria. Whether uric acid alone is the toxin in operation, Adam is of the opinion that between asthma and excess of uric acid there exists a very close connection. Previously suspecting that indicanuria and asthma might be concurrent, he made numerous observations, but these failed to substantiate the existence of any constant relationship between these two conditions. Adam concludes, therefore, that in certain forms of asthma there is a convulsive or spasm-producing toxin in operation upon the blood-vessels whereby are explained the paroxysmal attacks of difficulty of breathing, the diarrhœa and bilious vomiting that occasionally occur, and the peculiar nocturnal or rather early morning periodicity of the asthmatic seizures.]

On the part of the kidneys there exist important disturbances. Without speaking of ectopia, upon which I need not return, and whose mechanism is quite peculiar, albuminuria is extremely frequent, not only as a trace, but in measurably large quantities, in the form of a retractile coagulum when the action of heat is made to follow that of coagulating reagents. I have established it seventeen times in one hundred cases in my most recent statistics (I had said 13 per cent. for one hundred last year).

When the condition of the stomach has been relieved albuminuria diminishes, or even disappears, to return, however, on the least indiscretion of diet. It follows in a line parallel with that of the disease.

Can we consider the albuminuria as dyscrasic and arising from a vitiation of the general nutrition? Is it the consequence of irritation, or of inflammation of the renal tissue by toxic substances which it is eliminating? I do not undertake the solution of these questions.

Albuminuria is variable as regards its intensity and its persistence; it is most frequently curable. In certain cases it lasts for a long time, being the sign of a renal lesion. M. Tapret had pointed out the *bruit de galop* in a case in which albuminuria appeared to be associated with the existence of a dilatation of the stomach; the albuminuria having disappeared, the heart ceased to beat in accordance with the albuminuric rhythm; later on, it is true, cardiac troubles had returned. I have observed several analogous cases.

Peptonuria is frequent in dilatation; I believe I was the first to draw attention to it. While in the normal state, peptone cannot be discovered in the blood, either because it has been transformed into albumin in its passage through the walls of the intestine, or the liver has changed it, or the white blood-cells have laid hold of it. In certain people, the subjects of dilated stomach, it passes into and remains in the blood, and is dialyzed afterward in its passage through the kidneys.

Let us now put upon record the modifications of general nutrition in people whose stomachs are dilated. As a goodly number of the organs suffer, it is therefore not surprising that one should have to note loss of power, diminution of physical and moral energy, emaciation in the advanced phases, but often, also, lax obesity with pallor, abundant deposit of urates in the urine, increase of acidity of the urine, and the appearance of a red-wine coloration on the addition of perchloride of iron.

Inflammation may seize certain of the tissues; we notice phlebitis. I have, twice out of one hundred times, noticed spontaneous phlebitis, and I have insisted upon the importance of this point, which no longer permits us to accord to spontaneous phlebitis coming on in the course of a chronic dyspepsia the signification which Trousseau assigned to it. Purpura, which indicates fragility and bad nutrition of the vessels, is met with two or three times in every one hundred.

In short, I ought to recall the existence of modifications of the bony tissue in the neighborhood of certain articulations. I have insisted upon the frequency of nodosities on the phalango-phalangeal articulations of the fingers; they are formed by enlargement of the bases of the second phalanx; in some rare cases upon the anterior part of the base are seated two lateral nodules, as we see them in the rheumatic nodules of Heberden, which are always found at the third articulation. We often see the four fingers of the two hands present, simultaneously, these deformities. Nearly always the patients are astonished when we call their attention to these nodules; they consider that they have always had them. Sometimes, however, the parents know the date, approximately, of their appearance, after an absence from home, such as, for instance, their return from college. In some people pains are felt in the joints which have become deformed.

Sometimes other joints may be deformed. I have noticed, at the metacarpo-phalangeal articulation of the thumb, a swelling and pain. In cases much more rare I have noticed pain and swelling at the level of the wrist; we sometimes observe painful swellings of other joints, and, in particular, of the internal extremity of the clavicle. Out of the whole of the observations, I have noticed joint deformities twenty-five times in every one hundred, and in men, taken apart, thirty-two times in one hundred. They are susceptible of improvement, or of lessening if the stomach improve. I have seen oscillations running parallel with this condition.

What can be the meaning of these nodosities?

Some have said, in opposition to me, that they were the effect of rheumatism, just as dyspepsia is. But, really, there is no choice in this of rheumatic deformation. Chronic partial rheumatism affects the knee and the hip; the nodosities of Heberden are seated at the third articulation of the fingers. Asthenic primary gout and deforming rheumatism seize the wrists and the phalango-phalangeal articulations at once, and only secondarily the second articulations. Why do we not see, in dilatation of the stomach, other joints seized,—the knees and metacarpo-phalangeal? Otherwise the subarticular signs of rheumatism are wanting in those who, having dilatation of the stomach, are, at the same time, the bearers of nodosities on the fingers; it is only by a begging of the question that we attribute them to arthritism.

In any case, I maintain the reality of the following empirical fact: When you find people whose fingers present, at the level of the second articulation, the nodosities of which I have spoken, you will nearly always notice in them the physical signs of dilatation of the stomach.

We may see nodosities situated also at the second joint of the big toes; one is rarely led to seek for them in consultation, but, seeking them, I have found them in some cases.

Not only may other joints be affected, but the osseous tissue itself may suffer, even in the continuity of the long bones. Thus may sometimes be explained rachitis and osteomalacia. If in the child, rachitis, as M. Comby has said, may be one of the consequences of dilatation of the stomach, it has appeared to me in several cases that osteomalacia, in the adult, may receive a similar interpretation.

*En résumé,* it seems to follow, from the existence of so many organic and functional troubles in people the subjects of dilatation of the stomach, that there is created in the organism a special aptitude for the tissues to become inflamed, and for perversions of nutrition to arise, from which result fragility of some part of the tissues and changes in the form of others.

What has occasioned surprise among many physicians, when I have pretended to establish a relationship of cause and effect between dilatation of the stomach and the other symptoms which are associated with it, is the variety of these symptoms, which a simple change of form of that viscus is incapable of explaining to them. Numerous, however, are the local diseases which take their hold upon the organism.

For a long time past, since Beau and before him, we have known how dyspepsias cause an impression upon the nervous system, the feelings, movements, nerves of the vascular system, and ideation; we have admitted that certain nervous symptoms, contracture of the extremities, may be induced by gastro-intestinal trouble. Whatever the disease of the stomach may be, certain functional disturbances are sufficient to cause the development of dyspeptic coma, which, symptomatically, is identical with diabetic coma.

This coma has been seen in cancer, chronic ulcerative gastritis, and I have seen it in dilatation of the stomach. Jaksch and Senator have properly described it. There is, at first agitated movement, jactitation; then comes a gradual somnolescence, rapidly changing into coma. We notice a singular form of dyspnœa,—twenty or thirty respirations only per minute, but constituted by a deep and laborious inspiration, with great movement of the larynx and a moaning, panting expiration. The temperature is normal; the pulse small, frequent, and compressible. The odor of the breath recalls that of chloroform; probably it is due to the same substance as that which is exhaled in the breath of diabetics, since we find it in urine with the same chemical reaction. It has, besides, been also noticed in leucocythæmia and pernicious anæmia.

Is it astonishing, therefore, that severe nervous symptoms should be caused by a simple dilatation of the stomach?

What occurs in the chronic gastro-enteritis of infants due to a defective or premature alimentation? At first there appears green, acid diarrhœa, which excoriates the buttocks; then arise subsequent phenomena,—fever, cutaneous eruptions (erythematous, eczematous, and pustular), and, last, the peculiar nodosities of rachitis. These are, really, alterations of the bony tissue, induced by a primary disease of the stomach.

It has been accepted, but not without difficulty, that, the kidney being diseased, there may result from it general disturbances,—dropsies, nervous accidents, headache, pruritus, deafness, amaurosis, dyspnœa from functional trouble of the heart, but, also, modifications in the structure of the heart; hypertrophy of the left ventricle with, as a stethoscophic sign, reduplication of the first sound. It has been thoroughly acknowledged, because each fact was presented in an isolated and successive manner, that all these conditions, so varied, arise from disease of the kidney. I believe that, in the same manner with regard to dilatation of the stomach, we will come to recognize the fact that the accidents so varied which accompany it are really subordinated to it.

If I am of this opinion, it is because I represent to myself the kidney as an organ with a functional dignity inferior to that of the digestive canal; it eliminates matter without altering it; and yet, what disturbances its diseases cause in the organism!

What can it be, therefore, which is absorbed when the stomach is at fault, the functional derangement of which disturbs the whole intestine? How is it possible for its derangement not to affect the whole organism? Think of the physiological importance of the digestive tube. It introduces into the organism all the solid and liquid material,—all except oxygen,—and, before introducing the material, it must elaborate it. It has, therefore, not only to play the part of an emunctory, but its functional derangement must vitiate part of the emunctory apparatus and the cells of all the organism.

Some people are willing to admit the reality of the symptomatic grouping which I have indicated, but they do not consider that all the associated symptoms may be subordinated to the stomach; there would be links established between them and it, but no subordination. As in certain cases of dilatation we find reunited several symptoms which recall arthritism, nodosities of joints, migraine, neuralgias, sibilant bronchitis, eczema, and as arthritism determines dyspepsia accompanied by a certain degree of laxity of the stomach, we are forced to rely upon this coincidence, so as to say that dilatation of the stomach is only one of the consequences of arthritism, like the other symptoms of which I have just spoken.

But this assemblage of symptoms of an arthritic nature is only the small coin, as it were, of arthritism! They are disorders which may arise outside of the arthritism; they are not the grand, fundamental signs of the diathesis; it is, so to speak, *arthritis minor.* We have in this enumeration met with neither diabetes nor gout. These are two diseases which are not met with outside of arthritism; on the contrary, dilatation of the stomach is rare in diabetics and the gouty. They may, nevertheless, arise in such by way of dyspepsia, should they be dyspeptic, and yet great eaters; for they accumulate one meal upon the preceding one not digested; they thus take meals irregularly, and in too great quantity. I do not say that arthritism is not concerned as a predisponent in the pathogenesis of certain dilatations of the stomach. But there is another influence, the direct heredity of this organic disposition. We very often see a mother and her four children the subjects of dilatation. Is it because they live in common and in the same manner, and undergo the same hygienic trials? No; it is that there are families in whom the stomach has a congenital tendency to undergo dilatation.

In a ward in the hospital, out of ten patients taken at random, you will find three with dilatation. This frequency of dilatation in the class of people attending hospital, and which is less predisposed to arthritism, agrees little with the opinion that would see in dilatation of the stomach an affection of an arthritic nature. It is true that, in our time, men of the working class have borrowed from the governing classes a certain number of their faults and vices of hygiene. But I have little hope in convincing the generation to which I belong. When one has taken up a certain line of study he does not care to leave it to undertake another. I address myself, therefore, chiefly to those who are now receiving their education, and I ask them to affirm my statements. It is not by immediate discussion that one can settle such questions, but only by facts. And yet, among those who attack my manner of viewing them, how many of them are there who have ever thought of seeking for dilatation of the stomach in all their patients? Among those who may wish to do so, how many of them know how to do it? And, among those who can seek for the existence of a dilatation, how few are preoccupied with the greatness of the question? If we now examine under what appearances dilatation of the stomach is presented to us, we are led to recognize several clinical types of it.

There exists a *latent form;* it is the most frequent, since it constitutes two-thirds of the cases. No abnormal sensation is complained of by the patient; no functional trouble is revealed on his being interrogated. Only a careful examination of all the organs can alone enable us to recognize the physical signs of dilatation of the stomach. In the *dyspeptic form,* the patient complains of pains, of slowness of digestion, and often of constipation. The *hepatic form* is constituted by congestion of the liver, which shows itself by increased size in the volume of this organ and by a sensation of weight in the right hypochondrium. It is sometimes accompanied by jaundice, and frequently appears in young subjects, which is, perhaps, the explanation of the chronic jaundice of infancy.

There exists a form which simulates biliary lithiasis; pseudo-gastralgic pains, which are often really gastralgic, show themselves slowly, when intestinal digestion commences. Owing to the hydrochloric acid being deficient, acetic acid is produced in excess, and irritates the mucosa of the intestinal tract. We should include movable kidney rather in the renal form, although it depends upon repeated congestions of the liver.

To the *neurosal type* belong vertigoes, depression in the mornings, migraine, vascular spasms of the fingers, spinal irritation, cerebro-cardiac neurosis, hypochondriasis, and contractures of the extremities.

The *cardiac form* includes palpitations, breathlessness, beating in the temples, redness of the face, cardiac anguish, and false angina pectoris.

The *asthmatic form,* or bronchitic, is that in which coryza is frequent; in which glutinous expectoration, occluding the bronchial tubes, provokes laborious cough with sibilant sounds that disappear when the patient has succeeded in expelling the mucus.

The *renal form* it is very important to recognize. When we have established in a person an albuminuria which is not the transitory albuminuria of fever, and when we are undecided between the hypothesis of a lesion of the kidney and that of a cardiac affection, it is necessary to think that this albuminuria may be of dyspeptic and stomachal origin, since seventeen times in every one hundred albuminuria co-exists with dilated stomach. Simultaneously, the same accidents may exist as those which are under the dependence of other albuminurias,—cardiac hypertrophy, for example.

Under the name of the *cutaneous form* we may include urticaria, acne rosacea, and certain circumscribed eczemas, etc.

The *rheumatismal form,* although the word may be defective, is characterized by the predominance of joint manifestations, which at once attract the attention, and which are often wrongly looked upon as chronic rheumatism. To this form phlebitis is, perhaps, attached. I have seen it in medical men who had dilatation of the stomach and who considered themselves the subjects of rheumatismal phlebitis.

Last, there is occasion to admit an *acute or chronic consumptive type.* In the acute consumptive type the patient has always suffered in his stomach for ten or fifteen years, then he rapidly feels himself thoroughly exhausted, and soon after he is no longer able to leave his room,—not even his bed. The physician, finding no organic lesion, calls the case one of nervous fever. To the chronic consumptive type belongs the case of so many patients who in the hospitals pass either for idlers or hypochondriacs.

We could multiply these types, but around these ten may be grouped all the other symptoms. We must still remember the fact that dilatation of the stomach renders the economy more vulnerable, and opens the door to *diseases of debility. Chlorosis* in young girls and *pulmonary phthisis* are often induced by dilatation of the stomach. This latter exists in two-thirds of the tuberculous, and, if we have sought for it early enough, we can convince ourselves that the physical signs of dilatation have sometimes for long preceded the first symptoms that may be regarded as the premonitions of tuberculosis.

I am, therefore, fully of the opinion that dilatation of the stomach is the outcome of a veritable *acquired diathesis,*—a morbid disposition due to a disturbance of the general nutrition. Do we not see it, for example, induce alterations in the skeleton in the same way as that to which we attribute the production of rachitis? If it is true that in rickets it may be the formation of lactic acid in excess which hinders the calcification of the bones, in patients attacked with dilatation of the stomach the formation in the digestive tube and the absorption of acetic acid in excessive quantity perhaps explain the nodosities on the fingers. I have even seen osteomalacia produced; at least, the bones were painful at the level of the ribs, joints, femur, and pelvis. I have seen the pain increase by standing so as to render walking impossible.

[Since Bouchard wrote the foregoing the subject of gastric tetany following dilated stomach has received considerable attention. Although comparatively speaking a rare affection, it is extremely fatal, and yet if diagnosed and treated early a fatal termination may be warded off. The name *tetanie* was given to the particular group of nervous phenomena by Corvisart in 1852, but it is to Newman (*Deutsch Klinick*, 1861) and to Kussmaul (*Deutsch Archiv f. klin. Med.*, bd. vi, 1869) that we are principally indebted for what we know of the association of tetany and dilatation of the stomach. Of more recent writers I would mention the exhaustive paper by Professor Halliburton and Dr. John S. McKendrick in the *British Medical Journal*, June 29, 1901,—a paper not only interesting from the physician's point of view, but in which, on account of the completeness of its references and the results obtained by experiments upon animals, may be said to be focalized nearly all that is known of this very important subject. The symptoms observed in their patient, a man who had reached the middle term of life and who had suffered off and on for fifteen years from "his stomach," were pain after food, relieved by vomiting large quantities of sour-smelling material; occasionally hydrochloric acid was present in excess and sarcinæ were frequently found in microscopical examination of the vomit. For three years previously he had used the stomach pump two or three times a day. The symptoms of tetany had developed rather suddenly and without any apparent cause so far as change of diet was concerned; they were preceded by severe frontal headache, a sense of tingling and numbness of the fingers followed by spasmodic contraction of the fingers as in the "accoucheur's hand." Patient passed rapidly into a state of coma which soon cleared up after large intestinal injections and drastic medicines.

During the tetanoid seizures the urine contained a trace of albumin and acetone, and when the spasms subsided these gave place to sugar. The urine had a specific gravity of 1028. The vomit contained acetone; hydrochloric, acetic, and butyric acids; but no sarcinæ.

Albuminuria is not unknown in gastric dilatation and tetany. The symptoms, however, can scarcely be attributed to uræmia. After death the kidneys have been found to be healthy, but in a few instances these organs have been the seat of pathological changes. As the albuminuria is usually transitory, this circumstance suggests that it is due to the action of some poison in the blood upon the renal parenchyma. Nature, too, as we have stated, may be a temporary constituent of the urine. Other substances have also been found therein: *e.g.*, sugar (Fenwick), a picrin salt (Albu), and indican (Oddo and Sarles). In gastric tetany Gumbrecht found the uro-toxic coefficient of the urine increased.

With the object of ascertaining upon what particular substance absorbed from the stomach the nervous symptoms of tetany depended Halliburton and McKendrick injected preparations of the contents of their patients' dilated stomach into animals. This was followed by a marked fall in arterial pressure. On the supposition that this might be caused by the acidity of the gastric contents the fluid was gently neutralized by means of potash and when this was injected the fall of pressure was extremely slight. The presence of some acid substance therefore seemed to be responsible for the fall of blood-pressure, which occurred whether the vagi were intact or not, and was dependent upon some action either direct or reflex, upon the cardio-inhibitory center. Bouveret and Devic (quoted in Lancet, November 26, 1898) injected into the blood-vessels of animals varying percentages of hydrochloric acid. The normal amount of HCl in gastric juice is 0.2 per cent. Beginning with 0.1 per cent. solution, they proceeded to 0.9 per cent. solution; but it was not until 0.6 per cent. was reached that there was observed a fall of temperature in the animals. The injection of 0.9 per cent. solution of hydrochloric acid was followed by general convulsions and death, and at the autopsy a sero-sanguineous fluid was found in the peritoneal cavity. The dose of hydrochloric acid that is fatal is 0.4 per kilogram of animal. Weak solutions—*e.g.*, 0.2 and 0.3 per cent. —cause no inconvenience when injected into animals.

Halliburton and McKendrick's experiments show that the contents of a dilated stomach contain some material that is more poisonous than hydrochloric acid. Beyond saying that this substance has an acid reaction they do not attempt to define it further or to give it a name. It does not necessarily follow that the acid substance that is circulating in the blood and which is presumably the cause of the nervous symptoms of tetany should have been absorbed from the stomach. More than likely this acid may be the result of some faulty metabolism of the body caused by the circulation of toxic material absorbed from the gastro-intestinal tract.

It is still taught by many that the symptoms of tetany are due to dehydration of the tissues consequent upon the exhalation of large quantities of liquid through the gastric mucous membrane and the vomiting of large amounts of this watery material. It is to these circumstances that we must attribute the deficient amount of urine passed by the patients. The protoplasm of animal cells can only bear the abstraction of a limited amount of water, and therefore dehydration of the tissues may play a part in the development of the symptoms, but it is more probable that auto-intoxication plays the major part, since on almost similar series of symptoms is observed in diabetic coma when patients are not always emaciated.

What the poison is that causes gastric tetany it is impossible to say—Brieger is of the opinion that it is a peptotoxin. Bouveret and Devic injected into animals the toxin produced during the peptonization of proteids in the presence of alcohol and they found that it caused tetanic convulsions in large doses and in smaller quantities the ordinary contractures of tetany. It is believed that this peptotoxin is produced in a dilated stomach when there is an excess of acid, but it is not yet known whether it is an ethylamin hydrochlorate or an ethylene dianin. Gumbrecht speaks of the poisonous substance as an albumose. Without giving it a name, Halliburton and McKendrick describe the toxin obtained from the contents of a dilated stomach as having an acid reaction, soluble in alcohol and normal saline solution, and when injected into animals as causing, directly or indirectly, reflex excitation of the cardio-inhibitory center and probably of other centers in the brain and spinal cord.]

# LECTURE XIX.

## DILATATION OF THE STOMACH—ETIOLOGY, PATHOGENESIS, AND THERAPEUSIS.

Causes of dilatation of the stomach. Hygienic causes: excessive, permanent, or too frequent distension of the stomach, in consequence of bad alimentary hygiene. Pathological causes: catarrhal or interstitial inflammations; mechanical obstacles to the evacuation of the contents of the stomach. Physiological causes: insufficient innervation; congenital or acquired debility of the muscular tunic; reciprocal relations between typhoid fever and dilatation of the stomach; predisposition of those suffering from dilatation to contract typhoid fever.——Therapeutics based upon the knowledge of causes. General stimulants. Alimentary hygiene. Regularity and infrequency of meals. Substantial alimentation in small volume. Choice of foods. The unsuitableness of alcoholic drinks and of everything which keeps up excessive fermentation in the stomach. Why insufficiently baked bread is not easily digested. Recent researches upon the fermentation of bread.——Necessity for reducing the quantity of drink. How the dietary which I propose for dilatation of the stomach is not simply the dry regimen proposed by Chomel for dyspepsia due to the use of liquids.——Milk food as the preparatory regimen in the cure of dilatation. Mixed regimen of eggs and milk. Regimen of infrequent and complete meals. Nutritive enemata.——Antiseptic medication as an auxiliary to the dietetic regimen: chloroform-water, hydrochloric lemonade. Indications for washing out the stomach. Treatment of pyrosis and of ulcerative pastritis.——Advantageous result of the above-mentioned regimen: rapid disappearance of the most disturbing and most painful symptoms. Necessity for lengthened continuation of treatment, in order to arrive at a complete cure, which is not always possible.

IN order to place before you again, in a few words, all the knowledge we have accumulated upon intoxication of intestinal origin, I recall to you that, after having demonstrated their reality, I have shown you how intoxication may be the result of normal fermentation, if the kidney is diseased, and how, with a healthy kidney, intoxication may be produced by abnormal fermentation. Afterward, I have proved to you that intoxication of intestinal origin, from abnormal fermentation, may show itself in either the acute or chronic state. The time has now come for considering the therapeutics of this intoxication. I ought already to have dealt with, in a summary manner, intestinal antisepsis, having been almost of necessity led to it, in order to interpret uræmia and to study its therapeutics. I am now led to undertake this question, while studying the treatment of intoxication from chronic dyspepsia; that is to say, chiefly from dilatation of the stomach. But all the treatment of chronic intoxication of digestive origin does not lie in intestinal antisepsis. It is not sufficient to neutralize or to delay fermentations. Without neglecting the employment of charcoal, which fixes the products of putrefaction, of iodoform, and of naphthalin, which prevent these from developing, it is necessary to address ourselves to the physiological actions of the organism, in order to correct the functional disturbances of the digestive canal.

We ought, if we can, to act upon the disease which leads to fermentation in the digestive canal by referring to its causes, or to what is predominant in chronic dyspepsias,—that is, dilatation of the stomach. In eight cases of dyspepsia we find seven times an exaggerated distension of the stomach with an impossibility of retraction. The causes of this excessive, permanent distension are numerous. Some arise from faulty alimentary hygiene. Excessive distension, too often repeated and prolonged, leads up, more or less rapidly, to a forced condition of stomach. Individuals who eat too much or drink too often dilate their stomach, but other hygienic errors lead to the same result. To eat too quickly, when we come to table with an excessive appetite, due to irregularity in our meals, is hurtful, for a very fine mechanical division of food is indispensable for its digestion. Irregularity of meals has also for its consequence the leaving of only too short an interval between certain meals. A meal is then introduced into the stomach, which still contains part of the preceding one. These are all bad hygienic habits, which mechanically engender dilatation of the stomach. Other causes may also be in operation, such as bad teeth, which prevent good mastication.

We can remedy all these causes in the premonitory period, but when the stomach is thus dilated, what then? You will be able to advise a certain number of palliative measures, which will only bring to the patient a minimum of help, if you do not seek in the minute analysis of the elements of the morbid state those which therapeutics could attack with the greatest chances of success.

Mechanical distension sometimes follows from pathological causes,—from an antecedent dyspepsia having determined habitually too long retention of food in the stomach; from a chronic catarrh of the mucous membrane, preventing physiological secretion; cancerous or cicatricial constriction of the pylorus. The puckered cicatrix of a cured ulcer of the pylorus may progressively lead up, in quite a mechanical manner, to distension of the stomach, where digestion, nevertheless, is normal in operation. We may attribute a large share in the pathogenesis to debility of the muscular wall. General nervous debility—that state of irritable debility and neurasthenia which exist in hysterical people and in ataxics—causes variations in the energy of the central nervous system, whence there results distension; but this is rarely permanent. We notice, too, an intermittent distension in exophthalmic goiter, in convalescence from serious affections, after grief, prolonged indisposition, sad mental preoccupation. All these distensions have not yet become dilatation, but may end in it. It is also necessary to take cognizance of the radical debility of such and such a tissue in certain people, in consequence of which, in the pathogenesis of dilatation of the stomach, there is occasion given for the influence of heredity. It is certain that in the same family dilatation of the stomach exists in several individuals, without our being able to call to our aid, in order to explain it, a group of hygienic defects. It may be said of the stomach, as of the scrotum, which is habitually retracted in certain people, that there is a weak condition in some, owing to a natural muscular debility.

Last, debility of the muscular wall of the stomach may be the result of a morbid degeneration. The study of degenerations of the muscular wall has been made in the intestine by Blaschko, Sasaky, Nothnagel, and Schleimpflug. They have seen atrophy to be the result of fatty degeneration of the muscular tunic itself, consecutive to inflammatory affections of the mucous membrane, to intemperance, or to habitual alcoholic intoxication, to lesions of the intestinal and central nervous system, and, finally, to infectious diseases.

These causes are probably attributable to debility of the gastric muscular wall. It is developed after typhoid fever;

oftener it arises at the beginning and even before the commencement of the disease. It is not rare for typhoid fever to be developed in persons whose stomachs have already been dilated. I have seen, in the course of the last two years, twelve cases of typhoid fever in my practice at the hospital; that is to say, coming on in patients under treatment for another illness; twelve times was there question of patients the subject of dilatation of the stomach. We might ask the question, had dilatation prepared the way for the introduction of the infectious agent? I content myself, for the moment, by an empirical statement of the fact. The largest number of patients whom we treat in the hospitals for typhoid fever carry nodosities on the second articulations, which prove that dilatation was primary.

If these, therefore, are the varied causes which may take part in dilatation of the stomach, what resources may their knowledge furnish us with for their therapeutics? Nothing of consequence, save two things. If there exist habitually a condition of primary dyspepsia, aggravated recently, it will be advisable to combat this dyspeptic state, in order to allow the stomach to become retracted. If the nervous system should increase the retractility of what remains of healthy muscular fibers, general stimulants can indirectly give advantageous results; these will not cure, but they will aid in the cure. We may stimulate directly the nerve terminations in the gastric wall by simple bitters and by astringent bitters. We may give attention to the general nervous system in its cutaneous and peripheral expansions; we may prescribe dry or aromatic friction, change or air, high altitudes, sea-air. It is necessary to remove all care, preoccupation, and to procure distraction by traveling and pleasurable occupation. Distraction is particularly necessary during meals, which it is well to take in pleasant company. These are small measures, but their utility is beyond question. We might derive benefit from the cold or hot douche, or the shower bath, with ordinary water, or that containing sulphur or saline material. We need not ask how a cutaneous douche revives the stomach; it is simply a question of improving function. With a bad tool a workman may do pretty good work. Sulphurous and saline baths, sea-baths, cold baths, and baths of

Plombières may be useful. I can scarcely believe in the favorable influence of electricity, despite the results of which some have made a great noise. They publish at first the successful cases, and they forget to mention the others. Inhalations of oxygen sometimes answer well; these improve the appetite and stimulate digestion.

Last and chiefly, we must pay attention to alimentary hygiene. This includes the whole of the means which cause digestion to be rapid, and which thus prevent a protracted stay of food in the stomach. We may put it in the following axiom: *it is necessary that the stomach should be distended the least possible, least often, and for the shortest time possible.* We must first masticate well; consequently, certain buccal preparations are sometimes necessary. We must eat slowly, and without mental worry. It is necessary to abstain altogether from work immediately after meals. Fatiguing work is bad, even if it is physical work; what is useful is no longer repose, but muscular activity in the open air, without its being indulged in to the extent of fatigue.

There must be neither eating nor drinking between meals. The meals must be widely separated from each other. To eat once a day is impossible. If we only make two meals, should these be separated by twelve hours? No; the needs of the organism are much less during the period given up to repose. We must allow nine hours between the two meals as the interval by day, and fifteen hours as the interval by night. This infrequency of meals is sometimes sufficient to cause heartburn to disappear and the sensations of heat, and to arrest the emaciation of patients who should moderate their appetite in order to prevent their pains. As a rule, we must allow to patients three meals *per diem,* with an interval of eight hours between the two principal ones and four hours between the first and second. We must make exception for growing children. The hours should be, for example, 7.30 and 11.30 in the forenoon, and 7.30 in the evening. In the cases where this interval is not sufficient for the digestion of the preceding meal to be completed, it will be necessary to proceed with the artificial evacuation of the stomach.

The meals ought not to be copious, but substantial. It is advisable to suppress all that is unnecessary and made with water,—consequently, liquid foods. Yet it is necessary to give sufficient, and even a little more, because the organism may be obliged to eliminate an excess of solid material by the urine, which can only be done by the help of a determined quantity of water. We must never expose ourselves to the attempt to reach the limit on this side of which urinary depuration might be prevented. We would not allow liquids at other than meal-times; 375 grams of drink at each meal, or three-fourths of a liter in twenty-four hours, ought, in a general way, to be sufficient.

As digestion requires that the foods should be not only softened, but penetrated by the gastric juice, they must not be fatty. The stomach is not called upon to digest fat, but the latter might prevent the stomach from digesting what it ought, by preventing the hydrochloric acid of the gastric juice from softening, penetrating, and hydrating meat and other alimentary substances. It is better still to have the fat emulsionized, as in milk. The food ought to be as much divided as possible; we must, therefore, prescribe food easy of mastication,—not hard food, but cold or very well cooked meat and boiled fish. It is necessary to avoid, as much as possible, everything that may have a tendency to undergo fermentation,—alcohol, which furnishes acetic acid, acid substances, and certain parts of bread. Wine is certainly unfavorable, especially red wine, and, above all, pure red wine. But pure water is distasteful to certain people, and, as they no longer have any appetite, they lose weight if they are submitted to this regimen. In order to give the least amount of alcohol possible, we must advise to be added to water one-fourth of white wine, one-third of beer, or a teaspoonful of brandy.

Bread is generally badly borne by dyspeptics, but rice, barley, oatmeal, and unfermented pastes are allowed. As regards bread, we may allow only the crust or grated crumb. The reason for this restriction is this: Baking, having interrupted the fermentation of the dough, has not stopped it altogether; consequently, this fermentation reappears when moisture and temperature are again favorable to it. In thoroughly baked bread fermentation is, on the contrary, entirely stopped. What, then, is this fermentation of bread? The idea generally adopted on the subject is that which was clearly defined by Graham. In the presence of cerealin (diastase) starch is broken up into maltose and dextrin. Maltose, under the influence of saccharomyces minor, forms two sugars,—dextrose and lævulose. The two sugars, under the influence of the saccharomyces, ferment, producing alcohol and carbonic acid, which cause the bread to rise.

M. Duclaux, who has accepted this theory in principle, denies, moreover, the existence of alcohol in this fermentation. The question has been taken up again by M. Chicandart. The result of his researches is that, in dough in process of fermentation, we do not find either soluble starch or dextrin. The first part, therefore, of the theory of Graham falls. We do not find in it more sugar than in flour. We do not find alcohol either, but in the fermented dough there exist acetic and butyric acids, supposing we only employ gluten without starch, and lactic acid with pure gluten. We also find leucin, tyrosin, phenol; that is to say, the products of the fermentation of a nitrogenous substance.

What undergoes fermentation in dough is, therefore, the gluten, which gives girth to the products of acetic fermentation in the presence of a bacterium,—the bacillus glutinis. But this resists the temperature to which the center of the crumb is found to be carried during cooking; and it may, therefore, carry on in the stomach acetic fermentation. By the knowledge of these facts is explained the usefulness of unfermented and grated bread in the feeding of dyspeptics.

After having laid down the general rules for a dietary which has for its aim the attainment successively of functional amelioration, then the anatomical restoration of a digestive canal deteriorated by dilatation of the stomach, I proceed to state precisely the concrete formula of the regimen.

I remind you that meals ought to be taken at regular hours; that, if it is possible to obtain consent from patients for only two meals in twenty-four hours, these ought to be separated by an interval of nine hours; but that, as during the greater part of the time three meals are necessary, the intervals ought to be four hours between the first and second and eight hours between the second and third. Thus, the first meal will be taken, for example, at 7.30 in the morning, the second at 11.30, and the third at 7.30 in the evening.

The patients ought to take nothing between meals, and should strongly resist any impulses of hunger or thirst, when even this resistance would cause them suffering, and in spite of the momentary relief which satisfaction of these desires would appear to give them. We will frequently secure from patients this difficult resignation when we have clearly made them understand the necessity, and when we have dazzled them with the hope of a definite and absolute cure. Meals should be taken slowly, and mastication should be slow enough to reduce the aliments into pulp.

It is necessary to insist upon the prohibition of liquid aliments which dilute the gastric juice, and of fats which remove from the action of this juice the solid alimentary substances, and to insist, also, upon the advisability of eating only a little bread.

The early breakfast should not be abundant: an egg, cooked fruits, or marmalade,—neither bread nor drinks. At the second meal there should be cold meats (well cooked), hot meats (but broiled in preference to underdone roasts), meat-soups, boiled fish, eggs lightly cooked, eggs prepared in milk, milk in some way solidified, paste (*e.g.*, vermicelli); rice prepared in milk, or in soup, or with the juice of meat; vegetable soups (considered, wrongly, as increasing flatulent dyspepsia), cheese, compôtes of fruit. Of fresh fruits these only will be allowed: strawberries, peaches, and grapes. I do not know why they are better digested than other fruits by dyspeptics, but I indicate the fact to you as the result of experience. Other fruits should only be allowed cooked.

The important advice as regards drinks is resumed in the instruction not to drink at the first meal nor between meals, and not to drink at any of the two principal meals more than a glass and a half, each glass containing 250 grams ($^1/_4$ liter). In the summertime, for patients who perspire profusely, we should moderate, somewhat, the rule, in order to make some compensation for the loss of liquid. Drink should be, by preference, pure water; alcohol ought to be avoided, because it gives rise to acetic acid. But, our habits being repugnant to the use of pure water, we would advise the addition to the water of one-third beer or one-fourth of white wine; we would reject red wine, which contains too much alcohol and tannin, also the infusion of tea.

It has been wrongly stated that the regimen, thus formulated, was the dry regimen already laid down by Chomel. But the whole regimen, according to Chomel, was limited to the suppression of liquids. Mine proposes to satisfy three indications; to obtain these gastric distension should be slight, infrequent, and of short duration.

In order to bring about the first, I am willing to give sufficient alimentation in the smallest volume possible. I moderate the employment of water, both because it occupies space and dilutes the gastric juice. Chomel has seen dyspepsia from liquids which is real and which may coincide with certain cases of dilatation of the stomach, but not with all; the dyspepsia of liquids is not dilatation of the stomach.

The second indication requires that the meals should be infrequent.

The third is fulfilled by the employment of solid foods, easy to digest and very finely divided, in order that the surface of digestion may be increased. I exclude aliments easily transformable into acetic acid; that is why I reduce alcohol to a minimum; and I suppress bread, which I only allow transformed into crust or toasted.

This regimen, such as I have just formulated, presupposes that there is still great digestive power. In a certain number of cases neither meat nor farinaceous vegetables are digested. What is to be chosen, then,—the dry regimen? No; but milk diet, on condition of instituting it according to the precepts laid down by Cruveilhier for the treatment of ulcer of the stomach, in frequent doses and in small quantities, in order that its digestion may be rapid and complete. Milk diet is a preparatory regimen. We should begin with the quantity strictly necessary to prevent deterioration of the organism,—1 tablespoonful every two hours, if it is advisable; then 1 liter daily in ten equal doses; that is to say, 100 grams every two hours,—

from 6 or 7 o'clock in the morning to 10 or 11 o'clock at night,—nine doses in the day; one during the night. By increasing progressively each dose, we reach 2 liters in the twenty-four hours, which are sufficient for the sustenance of any man. Last, 2 $^1/_2$ liters, in ten doses of 250 grams, should not be exceeded. And then we should proceed, by insensible transition, to mixed diet. We add, first, a yelk of an egg to one of the cups of milk, then to several, which brings us up to ten yelks of eggs. At this period we would replace, at 10 o'clock in the morning, the cup of milk by rice-soup, barley, oats, oatmeal, or paste, but suppressing the cup at midday, in order to allow the stomach four hours to digest the soup. In the evening the same substitution should be made at 6 o'clock. After a week of these two light meals, suppressing four cupfuls of milk, we can then add a whole egg to the soup; then fish or cold fowl at the morning meal, and at that of the evening clear soup of potatoes. From this time onward we may boldly approach the diet of two complete meals in the twenty-four hours; then we may alternately add, if necessary, the small, supplementary meal of the morning.

Sometimes from the first it may be necessary to maintain the patient a little more, if his weakness is excessive, or to beguile his thirst. We may have recourse to alimentary drinks or to nutritive enemata. We may employ aqueous solutions of peptones, properly prepared, which we now find procurable in France, and which have nothing in common with the products falsely sold for a long time under this designation. Or shall we be obliged to have recourse to alimentary powders (to meat powder), which have been of signal service in certain diseases in which it was necessary to maintain nutrition? I do not think so. They have, doubtless, the advantage of being very finely divided, but they remain difficult of digestion, because they nauseate. We cannot dispense with the part which the nervous system plays in the cure of the diseases of the stomach; the patient who swallows with dislike does not digest. It would be better, in case of need, to allow any fine pulp of cooked meat.

In order to prevent the excessive fermentation which dilatation of the stomach favors, we should have recourse to the antiseptic method. Many antiseptics are at our disposal. Creosote (which has been employed for more than thirty years, in acid dyspepsias particularly), iodoform, and naphthalin fail, very often, because they spoil the appetite; salicylic acid, in a sufficient dose to be truly antiseptic, induces nervous derangements; salicylate of bismuth, less soluble, is also less active. Chloroform water is better; oxygenized water is good; but what is better still is hydrochloric acid, which prevents anomalous fermentations and aids physiological digestion. No fermentation is possible in a liquid which contains for every 1000 parts 1.10 grams of anhydrous hydrochloric acid, equivalent to 3.30 grams of the fuming hydrochloric acid of commerce. The liquor which I employ is a solution with this formula:—

| | |
|---|---|
| Fuming hydrochloric acid, pure.......... | 4 grams. |
| Water .................................. | 1000 grams. |

It is, generally speaking, neither disagreeable nor irritating. It is a little painful to some patients,—cancerous particularly, or those who have ulcerations lying upon the great curvature. We may give it at one meal, only in the dose of a few mouthfuls during the course of the meal, or a glassful at the end of it. We may give as much as 750 grams of the solution apart from the meals. When digestion is not terminated three or four hours after the meal, we must come to the aid of the stomach by replacing its exhausted secretions. As a help, I ought to speak of the practice of washing out, so much in vogue for the last few years. It has given satisfaction on the old erroneous idea that fluids which have accumulated in the stomach ought to be removed. The real service which it renders is to free the stomach of the remains of previous digestions not attacked by the gastric juice and undergoing putrefaction.

Washing out the stomach does not cure dilatation, it can only relieve some of its consequences; and, as for its advantages, these are accompanied by certain inconveniences,—*e.g.*, the diminution of the appetite and of digestion, and, in consequence, increase of emaciation. Nevertheless, it is a necessary method under certain circumstances. We ought to lay it down as a principle that we should never introduce an additional meal into the stomach when the previous one has not been digested. Five hours after ingestion the presence of food in the stomach is pathological, and from the sixth hour onward there will occur in this alimentary mass anomalous fermentation. Beyond the seventh hour the alimentary residue will undergo exclusively acid or putrid fermentation. When, therefore, rational signs or exploratory catheterization shall have established stagnation of the alimentary residue in the stomach, there will be formal reasons for evacuating it. Then we can leave the stomach to rest for two hours, to recover itself, so to speak. Patients undergoing lavage ought to have only two meals *per diem.* At the same time you should make antisepsis; but, in order to attain this end, no liquid is necessary. We cannot introduce hydrochloric acid into an empty stomach, especially as, in these cases of putrid stagnation, there exists already upon the greater curvature punctated hæmorrhages and ulceration of the mucous membrane. But there is no inconvenience whatever in introducing iodoform (in pill), creosote, or nitrate of silver, which may be useful in overcoming pyrosis. This extremely painful symptom yields, too, generally speaking, after a few days of regimen, without the employment of medicines.

When pain is such that, in spite of the stoicism which you would like to inspire in your patient, it is necessary to intervene to give him immediate relief, we can neutralize the corrosive acids which cause such great pain by means of sodium bicarbonate, prepared chalk, calcined magnesia, charcoal, to all of which may be added a small quantity of opium or combined with chloroform water, which relieves pain and checks fermentation; finally, cocaine may render some service in diminishing the sensibility of the mucous membrane. When ulceration of the stomach supervenes, the therapeutic indications are those laid down by Cruveilhier. The patient is then in a grave condition, having reached a very advanced stage of the illness.

In making an abstract of the cases in which patients come to you only in the last stages of their illness, you will derive great benefit always from the dietetic and therapeutic rules which I have just laid down. You will sometimes see patients who have suffered for ten years lose their suffering at the end of two days, and declare themselves cured at the end of three weeks. Remember that this is not even an apparent cure, and that all the symptoms will reappear on the day following that on which the regimen has been abandoned.

At the end of what time, then, can we hope for a cure? In the case of certain stomachs, dilated from the period of infancy, cure will never be realized; but, thanks to the permanence of the treatment, we can overcome the anatomical imperfection of the organ. The largest number of patients can, nevertheless, be cured, but not in less than two years; and these cures are easily broken. Long before the cure of the gastric symptoms you will, fortunately, have the satisfaction of seeing disappear the superadded diseases, unless phthisis is part of the morbid process and the mushroom bacillus has developed upon the waste which the organism has supplied to it. There are nervous symptoms which may yield at the end of a few hours, even certain sibilant râles of bronchitis, which arise from intoxication, and are due to gastric fermentation; certain anginal cardiac symptoms (dyspnœal), and the cutaneous, and especially renal, manifestations. Albuminuria rapidly improves and totally disappears, at the same time that it is accompanied by cardiac reduplication. The alterations in the joints, caused and maintained by the excess of acetic fermentations, may even retrocede.

[1] The possibility of obtaining similar results is a reason, in my opinion, for insisting upon the indications to be fulfilled and

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[1] Since these lectures were delivered, M. P. le Gendre has studied more particularly certain points in the history of dilatation of the stomach, and he has published the result of his researches in an inaugural thesis, "Dilatation of the Stomach and Typhoid Fever. Semeiological Value of the Nodosities of Bouchard."

M. le Gendre has commenced by fixing the mean capacity of the stomach of the adult, estimated in cubic centimeters of water, basing his remarks upon an examination of 60 stomachs of cadavera taken haphazard; he believed that he might conclude that this average was less than 1300 cubic centimeters. But in 12 cases, in which he had made the autopsy upon subjects in whom dilatation had been diagnosed during life by "splashing" as the method adopted for diagnosis, the stomach had a cubic capacity of from 1450 to 3600 cubic centimeters.

M. le Gendre has described very minutely, from a morphological and anatomical point of view, the knotty condition of the phalangothe rules to be followed in the treatment of chronic intoxication of a digestive origin, the type of which is dilatation of the stomach.

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phalangeal joints of the fingers, the semeiological value of which I have made known. In what refers to those who are the subjects of dilatation, and are predisposed to contract typhoid fever, I am reminded that, in 19 cases of this disease which have come under my care within the last two and a half years, the contagion had exerted itself nearly always upon patients attacked with dilatation of the stomach; it had even attacked 4 authentic cases of relapse of typhoid fever,—facts certainly very rare concerning the subjects of dilatation. He draws attention to the relative frequency with which we meet with tænia and the lumbrici in individuals whose stomachs are imperfectly fulfilling their functions; which shows that the digestive canal of the subjects of dilatation is particularly favorable for the lodgment of disease-producing parasites, large or small.

M. le Gendre finally insists upon the very peculiar frequency with which we observe, in those the subjects of dilatation, certain morbid conditions badly classed in nosology,—afebrile or febrile gastric obstruction, continued febricula, synocha; choleriform, gastro-intestinal catarrh,—many of which are, perhaps, attenuated forms of typhoid fever.

# LECTURE XX.

## AUTO-INTOXICATION OF INTESTINAL ORIGIN—TYPHOID FEVER.

**Part played by auto-intoxication in typhoid fever. Typhoid fever is caused by an infective agent. History of the research after the pathogenic agent of enteric fever. State of the question. My own researches. The infective nature of typhoid fever, although not absolutely demonstrated, is probably absolute.——Besides the general infection of the economy by the pathogenic agent, the intestinal ulcerations are a cause of intoxication, either by increasing normal fermentations or by the induction of anomalous fermentative processes.—Rôle of secondary infections arising from the migration of common infective agents outside of the intestine, and of superadded infections, by penetration into the debilitated economy of special pathogenic agents: parotiditis, erysipelas, gaseous gangrene, furuncle, anthrax.——Rôle of increased temperature from the point of view of therapeutic indication of the part played by inanition. Therapeusis of the accidents of auto-intoxication of intestinal origin; disinfection of fæcal material by charcoal. Antisepsis of the intestine by iodoform and naphthalin. Part played by purgatives. Influence of intestinal antisepsis seen in the diminution of mortality.**

THE study of intoxication of intestinal origin does not appear to lead naturally to a digression upon typhoid fever. This is an infectious disease, and not a toxic one, and yet, when we come to study its therapeutics, it is necessary to deal with intoxication. In typhoid fever, in short, there come into play not only the minor vegetable organisms which, by one means or another, produce all the disorders which an infective agent can cause. By the side of infection there is evolved a secondary process,—an accessory one,—which is subordinate to intoxication. Well, then, were it only for this alone, therapeutics ought to concern itself with intoxication in typhoid fever. The primary cause of abdominal typhus is certainly regarded as an infective agent, and this enters by the intestinal canal; all that we know of its mode of transmission authorizes us to believe this. But the infective agent only exists transitionally in the digestive tube; that is not its habitat. The place where it is developed is the lymphatic system,—the closed follicles, Peyer's glands, mesenteric glands, and spleen. It may be eliminated by the intestine, landing there at the moment of necrosis of Peyer's patches, and be carried away by alvine discharges.

The organism which may be the infective agent of enteric fever has been known for a long time,—since 1871, by Recklinghausen; then by Klein, Sokolof, Browitz, and Fischl, in 1878. I myself found it in 1879, and I communicated in 1880 my researches. I have found it in all the pathological liquids, with the exception of sudamina. It is a rod possessed of the power of changing its form frequently,—a bacillus one day, disposed, later on, in the form of beads, then as isolated micrococci. We find it, at the autopsy, in certain organs,—the kidneys, spleen, and glands. During life I have found it in the urine; this fact was a novelty at that period; it led me to form the conception of infectious nephritides. I have said that, detected in the blood and urine, the microbe leaves its habitat to be eliminated by the renal emunctory. This fact has been confirmed since by Letzerich, who saw one form of the microbe,—the coccus; then by Eberth, who saw it in the form of a rod; and, finally, by Klebs, Meyer, Friedländer, and Gaffky. But does this fact, although agreed upon, prove that the microbe is the pathogenic agent of typhoid fever? Certainly not; it is necessary that we should have proved its presence in all individuals; that we should have isolated it by successive cultures, which deprive it, by degrees, of all that has been borrowed by it from the patient or the cadaver; and that in inoculating its descendants into animals we reproduce in them the disease with all its characteristics. Besides, we cannot raise objections to the method that the organism, even isolated and cultivated, has not caused the disease. Negative results do not prove that this organism may not be the pathogenic microbe. Do we know that there exists an animal species liable to contract typhoid fever?

In every case the result of inoculations have been always negative; the cultures made from all the humors, with the exception of sudamina, have been successful. I have inoculated them into the rabbit, serpent, cat, dog, and pig, and I have introduced them by the digestive canal, by subcutaneous methods, and intravenous injection. I have inoculated quantities of the culture fluid which are far from being weak, and which certainly contain milliards of bacteria.

I have readily produced in the pig a feverish illness, with an evening rise of temperature, in which the thermometric curve is broken up into a series of ascending oscillations—a stadium or plateau—and a line of descending oscillations. Recovery took place in the two pigs operated upon. Had they had a bastard typhoid fever? In these cases I ought to have communicated to them immunity for the future. Yet fresh intravenous injections of typhoid cultures have caused in them renewed pyrexia similar to the first. Typhoid fever being a disease which creates immunity, the anatomical lesions which are characteristic of it in man, not having been established in other inoculated pigs which have not recovered, I am forced to admit that the disease which I have communicated to these animals is not typhoid fever. Things remain, therefore, at the point in which they were before these experiments, and I have no right to teach that typhoid fever is a parasitic disease, like anthrax or glanders.

Thus we have had, so far as the subject of the infectious nature of typhoid fever is concerned, only probabilities. An important argument is that typhoid fever is transmissible,—contagious. As a general rule, we do find a relationship between cases. A patient who has come to a district becomes a center from which radiate other patients, who scatter the disease in the healthy localities. Transmission especially occurs, as we know, by the dejecta, and mediately through the drinking-water which the dejecta have impregnated. Thus it is that, calculating upon clinical and etiological facts, and not upon microscopical, we have come to regard typhoid fever as the result of the introduction of a parasitic agent into the organism. But, besides general infection, the disease induces local effects. The most remarkable are the intestinal lesions, consisting in ulceration and in gangrene of certain parts of the intestine, then in excessive putrefactions, which are in this way developed, showing themselves by meteorism and a fetid diarrhœa. I do not say that these putrefactions arise from the presence of a pathogenic organism, but we have reason to believe that it operates upon the normal excessive fermentations in the intestine, besides the anomalous fermentative processes of which the organs are the seat.

If the fæcal matter of a man in health is toxic, in typhoid fever the unusual intensity of normal putrefaction may easily add something to the infection, and we may conceive how, from such a source, there must be some notice taken of intoxication in the treatment. We must deal, too, with the secondary infections arising from the migration of ordinary infectious agents from the intestine and from the surface of intestinal wounds into the blood and the tissues, where their multiplication is favored by want of resistance of the latter. It is probably these common infectious agents, on the move, which cause certain forms of abscess, furunculosis, anthrax, and externally ordinary eschars; also in parts of the body which are not subjected to pressure certain spontaneous forms of gangrene arise, perhaps from the action of common infective agents upon the tissues, where their influence for harm is no longer counterbalanced by the activity of the circulation and nervous system.

We sometimes see, in the course of typhoid fever, certain infective processes superadded, such as parotitis. Inflammation of the parotid is produced by ordinary infective agents, which are introduced by the excretory salivary ducts; and this occurs as much by other glands,—*e.g.*, by the kidney when it is no longer in function, and when the bladder is the seat of inflammation (miliary abscess; surgical kidney).

Erysipelas is frequent in the advanced periods of typhoid fever. We may even see it cause gaseous gangrene. In certain cases the eschars from the decubitus of the patient are the point of departure of an emphysema which extends some distance. I have seen a case in which gaseous gangrene has been the cause of death. It is not simply enough to conceive of typhoid fever as the result of a general infection by putrid intoxication derived from the digestive tube, or of secondary infection, and of superadded infection; we must consider it along with one of its necessary effects,—the fever. It is impossible to build up a systematic treatment upon one pathogenic view only. Doubtless, if we could at once destroy the pathogenic agent, this great blow would be decisive and would put an end to the fever, as also to all the fatal accidents. But, since we cannot attain this end, we must, I repeat, reckon with the fever, and, if this becomes of itself dangerous, try to reduce it.

We are here in the presence of a continued fever,—which is, without intermission, destroying the patient for weeks,—which is higher than 39° C. (102.2° F.), which brings about unusual metamorphoses in living matter, depriving it of oxygen; induces modifications which are subversive of nutrition and perversive of disassimilation. This excessive temperature produces effects which are harmful to muscular fiber and the nervous system. Sometimes the patients die simply from the persistent hyperthermia. The physician has not, therefore, only to deal with the cause of the disease. When he cannot suppress that, he ought to struggle in succession against all the effects arising from this cause.

During the long course of this fever inanition is extreme. The patient, taking no combustible material from the outer world, lives upon his own tissues. He finds that it is impossible for him to digest. We cannot, therefore, nourish him like another person; still, we should try, by ingenious means, to introduce into his organism combustible material, and not allow him to destroy his own tissues.

As many as are the indications to be fulfilled in the treatment of typhoid fever, just as many are the difficulties to be overcome. We must, so to speak, lay siege to the disease and attack it at all points where it appears vulnerable. Yet I have only laid down general indications; there are still special indications for such and such a disease, such and such a particular accident.

I now come to the therapeusis of the accidents of intoxication of intestinal origin. In the last ten years I have been giving charcoal to neutralize a part of the toxic products. More recently, I have completed this method by the addition of means to prevent the fermentations which develop toxic products. I will tell you some results which I have obtained in these two phases of my practice:—

With charcoal I have deodorized and discolored completely fæcal matter; I diminished their toxicity, and the alkaloids found are no longer but in insignificant quantity in the filtered liquid. These first effects some have denied. It has been said, in one of the learned societies, that charcoal was not an antiseptic substance, without it being known for what reason I was employing it. Besides, it has been stated, too, that charcoal does not succeed in disinfecting; yet we have had proof of all that I have said, by giving 2 grams of charcoal in medicated cachets. As for myself, who gave 100 grams daily, spoonfuls by the mouth every two hours, I have obtained liquid stools,—black, odorless, and not resembling fæcal matter. Such matter has not only optical and olfactory properties which are less disagreeable, but intravenous injections show that they are much less toxic; their toxicity is found reduced by four-fifths. Not only is the matter contained in the intestine less toxic, but a consequence easy of demonstration is that the individual is not poisoned, for the toxicity of his urine is found considerably diminished. The urine remains toxic owing to the products of alimentation or of disassimilation, but they are no longer convulsive. We must employ from 90 to 120 cubic centimeters of urine in order to kill 1 kilogram of animal.

Owing to the disinfection of the stools, we also obtain other beneficial results. The patients have no longer the earthy complexion, but a clear skin, white and red; the intestinal distension diminishes; the tongue remains moist; eschars are extremely rare.

Finally, statistics resting upon more than 300 cases have shown that the mortality had fallen to 15 per cent., instead of 20 to 25 per cent. In these statistics I include all the cases, without exception, which have come under my hospital care: the patients who have not been submitted to this treatment are those who have come with an intestinal perforation or have succumbed to slow complications. I would be perfectly right in deducting all these patients, in order to judge of the value of the treatment by itself; but I have not done so in order to establish a comparison with other methods. I take the total mortality, *en bloc,* of the hospitals of Paris.

For the last two years I have added, to disinfection, intestinal antisepsis. After numerous attempts, after having employed creosote like Pécholier, salicylic acid, and mercurial preparations, I have returned to the true principles of intestinal antisepsis by applying substances capable of acting throughout the whole length of the digestive canal; that is, insoluble substances,—the salicylate of bismuth, iodoform, naphthalin. I have only employed phenic acid to wash out the large intestine, morning and evening. I have caused to be given a carbolic enema of 1 in 1000, except in the case of infants, where this sometimes causes a collapse rather disquieting in appearance; in the adult, even, one has seen perspiration, faintness, almost coma. With the doses to which I have alluded, these accidents are very rare; they may be such as to cause a little fear, but they are not grave.

I cause to be taken daily by my typhoid patients 1 gram of iodoform, finely powdered and representing a surface of 60 square meters. I obtain, by this method, as the fæcal matters are deodorized and discolored, a diminution of the alkaloids which the filtered liquid contains, a diminution of the toxicity of the fæcal matter, the almost complete disappearance of the agents of putrefaction. Microbes are no longer found in the alvine secretions, save in very minute quantity. The tongue of the patient is never dry.

The mortality in the same hospital, in the same quarter, with the same physician, has fallen to 10 per cent.,—an index at once consoling. The partisans of the cold-bath treatment are proud enough with this index of 10 per cent., but I have reached it without baths.

I have taken care to add to the preceding methods a purgative every three days,—a glassful of Seidlitz water,— and I never abandon the treatment without subsequently causing a clearing out of the intestine by a purgative. Otherwise, there may be produced in the large intestine a hard accumulation, capable of causing alarming obstruction, with fæcal vomiting. This purgative is castor-oil, administered to the patient in a small dose, while he is in a bath.

Such, then, are the principles of the antiseptic method applied to the digestive tube of patients attacked with typhoid fever. For one year I combined naphthalin with iodoform; the time has not yet arrived for me to be able to judge of the value of this new method of medicinal treatment.

# LECTURE XXI.

## PATHOGENIC THERAPEUSIS OF TYPHOID FEVER—ANTISEPSIS OF THE INTERNAL MEDIUM.

**Is general antiseptic medication theoretically admissible? Can we destroy infectious agents in the economy? Antisepsis of the internal medium. Refutation of objections.——Substances capable of preventing the multiplication of infectious agents that are vegetable are not necessarily fatal to animal cells: the aspergillus, for example. The antiseptic action of medicaments is not paralleled by their toxic power. Therapeutic and antiseptic equivalents.——Antisepsis is proposed not so much in order to destroy microbes as to prevent their reproduction. A simple change of the medium is sufficient to cause large vegetables to become sterile.——Experience has demonstrated the utility of employing antiseptic medicaments. Specific medicaments are all antiseptic. Mercury. Quinine. Salicylic acid. Phenic acid. The largest number of medicaments called antipyretics act, perhaps, only as antiseptics.——Attempts at producing general antisepsis in typhoid fever. Mercury may, perhaps, shorten the duration of typhoid fever. Its inconveniences as the exclusive method.**

I CONTINUE the study of the therapeutic indications in typhoid fever. Beyond internal antisepsis, of which I have shown to you by statistics the incontestable advantages, is there not something to do from the point of view of real general antisepsis? Is there a therapeusis rigidly pathogenic of typhoid infection? This disease may serve as an example to us more than any other in order that we may judge of certain questions of general therapeusis. Apropos of it, we may study the principles of the antiseptic method, of the antipyretic method, and the rules which should regulate the feeding of patients in infectious febrile diseases.

I am anxious to declare that I do not substitute the antiseptic method for the antipyretic in the treatment of typhoid fever, and that I have not the desire to suppress all that has been done in the way of antipyretic medication, in order to attempt to substitute, for real and serviceable results, that which is still hypothetical and irregular in its effects.

But if it is good to attack hyperthermia, which is a source of continual danger in fevers, it is permissible to attack it in its origin; and in those maladies whose cause is the penetration of vegetable organisms into the system, does it not become us to seek for that which we ourselves can oppose to their presence and multiplication? Can we, definitely, in infectious diseases, effectually attack the infective agent?

Some have denied that this is possible. And yet the question has been settled in the affirmative by surgery. We can no longer discuss here the possibility of suppressing septic agents. We are now dealing with infection of free or unbroken surfaces, on which infectious agents multiply; on which are accumulated toxic substances,—infective agents which may proceed to form colonies in various organs, and poisons which may cause elsewhere secondary functional derangement. It is, besides, through the imitation of that which surgeons have obtained that I have demonstrated the possibility of effecting intestinal antisepsis. In medicine, we can still quote the example of certain diphtherias which remain for a time infectious on the surface, and to which antisepsis of the surface is applicable.

When we are dealing with patients in whom the infection is no longer on the surface, but one of general infection, things are presented, it is true, under another light. Sometimes it is the blood which may be the natural habitat of the infectious agents as in anthrax and relapsing fever. Sometimes the pathogenic agents are localized in the tissues. In every case one must succeed in impregnating the whole organism with the antiseptic agent.

But do we not injure, at the same time, the animal cells This objection, which appeals to sense, has been from the firs the principal reason why the opponents of antiseptic medication have never supported it. It has been formulated in a startling manner when it has been said, "We aim at the microbe and w strike the patient." Nevertheless, this masterly expression, fo which I entertain respectful esteem, is, at the bottom, only sophism. We can answer, actually, that what is hurtful to on vegetable cell is not always hurtful to another cell of an anima nature. Thus, is there not a whole series of pathogenic agent which are killed by a substance indispensable to the animal, viz oxygen (they are, unfortunately, not the most numerous)? W cannot, therefore, say that what will kill the microbe will necessarily destroy the patient. We can, besides, support the argument by the experiment of Raulin, who has shown that silver, in an almost infinitesimal dose, is opposed to the development of the aspergillus. Here, then, is a substance fatal to certain vegetable cells in a dose not at all hurtful to animal cells. On the contrary, certain inferior vegetables live preferably in media poisonous to the animal (solutions of quinine, arsenic, and antimony in doses fatal to man). We must, therefore, differentiate antiseptic substances so as to state precisely those which are very hurtful to vegetable cells, and yet innocent so far as the elementary tissues of the animal are concerned.

The antiseptic action of medicaments does not proceed in a parallel manner with their toxic power. Bert was wrong in identifying the nerve cell with the cell of the ferment. To say that what is hurtful to a vegetable cell ought to injure, *a fortiori,* a nerve cell, is only true for certain cases and in certain conditions. Aniline is toxic and antiseptic. Phenic acid is equally toxic and antiseptic. But is there any parallelism between their toxicity and their antiseptic power? Aniline is five times less antiseptic than phenic acid, but four times more toxic for animal cells.

Can we compare, from the same points of view, phenic acid with mercury? With the same toxic power, phenic acid is six times less antiseptic than the salts of mercury. The choice of these second substances is imposed upon us, therefore, when we wish to obtain maximum action against microbes and the least against the animal elements.

Not all mercurial salts have an antiseptic action proportionate to their toxicity. The biniodide, eminently antiseptic, is less toxic than an equal weight of the bichloride.

The iodides of potassium and sodium are moderately antiseptic. To prevent the fermentation of a liter of soup, we must add to it 48 grams of iodide of potassium or 50 grams of iodide of sodium. The action that is hurtful to the ferment is then sensibly the same for these two bodies, but the iodide of sodium is but one-fortieth as hurtful to the animal as iodide of potassium.

It is advisable, therefore, to compare therapeutic equivalents of medicaments and their antiseptic equivalents. We can also derive benefit from the combination of different antiseptic substances. If we wish to administer, simultaneously, two or three antiseptics, it seems that we must—in order not to run the risk of causing intoxication—not give any one of these bodies in more than one-half or one-third of the dose which is the limit of their toxicity. I have observed that we can go beyond these fractions. In choosing antiseptics and in associating them, we can double the antiseptic power and only increase by one-third their toxic activity. Such a vegetable organism is not otherwise influenced by an antiseptic agent which kills other vegetables. There is room, therefore, for fresh experiments; but it is advisable to follow these therapeutic attempts, relying at first upon the experimental method in animals.

I have tried to make experiments with antiseptics upon the infective agent of typhoid fever, or at least upon its assumed pathogenic agent whose culture is easy in the neutral soup made from beef; its sensibility is greater to the action of biniodide of mercury than is that of the bacterium of fermenting soup,—a long bacterium whose sensibility is as 2, while that of the typhogenetic agent is 3. Finally, as a last argument, it is said in objection that we cannot kill pathogenic bacteria without destroying the cells of the patient. But what we propose is not so much to bring about death of the microbes in the depths of the organism as to prevent their multiplication. It is one thing to destroy an individual and another to render him sterile. I borrow a convincing example from botany. A palm-tree from Biskra, which covers itself with fruits destined to ripen when it grows to the limit it would have attained in the desert, can live quite well in the greenhouses of the museum, but it will never develop within them fruit capable of reproducing itself; it will not even bear fruit in Algeria. Thus, a simple modification of the medium, while leaving to vegetable organisms their vital integrity and all their energy, can render them incapable of multiplication. The liquid of a malignant-pustule culture inoculated into sheep belonging to Beauce will cause death in all of them, but if sheep of the same breed are taken to Algeria, and are inoculated with the same culture, nineteen inoculations out of twenty will remain sterile. What is true with regard to large vegetables is also true of the smaller. If we pass to the application of this idea of reproduction, it is perfectly immaterial whether man is rendered incapable of multiplying cells during his illness; but if we can prevent the cells of his parasite from being multiplied, the disease ceases, for it is not caused only by the presence and development of the ferment, but by its multiplication. Let us propose to ourselves only to oppose the latter, and let us merely try to impede the activity of this multiplication.

*En résumé,* general antisepsis is theoretically admissible, and we have no right to refuse its admission by an *a priori* exception. What it requires now is not argument; facts are necessary to establish, and that thoroughly, the employment of antiseptics which have impeded the course of certain infectious diseases.

Well, has experience not already produced an opinion? Is syphilis cured by the antiplastic virtue of mercury? We can scarcely maintain that to-day. In intermittent fever, is it as an antithermic that sulphate of quinine brings about a cure; and in rheumatism, salicylic acid?

Quinine brings about a reduction of temperature in an important and useful manner in three diseases only: intermittent fever, typhoid fever, and one of the forms of puerperal fever. In a healthy man it increases it by some tenths of a degree; it does not reduce it in other febrile diseases. In fibrinous lobar pneumonia 3 to 4 grams of quinine produce quinism without reducing the temperature more than one-half a degree. In the subject of pleurisy the effect is not more marked. In erysipelas you do not reduce the temperature even with large doses of quinine. In the diseases in which quinine acts, it is only by acting in opposition to the infective agent that it causes a cessation of the fever which is the consequence of it.

It is not so with phenic acid. Phenic acid reduces temperature by its physiological properties; by its action on animal cells it diminishes calorification and also acts upon the vegetable cells of infectious organisms.

An enema containing 48 grams of crystallized phenic acid was administered to two of my patients, at intervals of two minutes between each injection. The mistake was made by attendants who were new to the work. The first patient uttered loud cries while the solution was being administered to the second. The nurse, being alarmed, ran for the house-surgeon, who ordered the bowels to be immediately washed out with 15 liters of water. The patients were already in a state of coma, in which they remained for several hours, their temperature being 35° C. (95° F.). One of them had a temperature of 40° C. (104° F.) before this accident, the other was convalescent; the first rose to 41.8° C. (107.4° F.) in the evening, and in the same time the other reached exactly the same temperature; the one that had a temperature of 40° C. (104° F.) was apyretic the next day with a temperature of 37° C. (98.6° F.), and remained convalescent; the disease was destroyed, but the patient was nearly killed. This is also true of alcohol; I observed it in the case of a young woman who had caught typhoid fever in Rome. She was having injections of 1 in 1000 of phenic acid. The Sister of Mercy, by mistake, one day administered an enema with alcohol at 80° C. (176° F.). Her malady had reached the ninth day; the first lenticular red spots were appearing. Her temperature fell to 35° C. (95° F.); she was delirious and totally blind. When the temperature returned to 37° C. (98.6° F.), it remained at this point for four days. The malady resumed its course; the microbes had merely been dormant; they required a certain time to reproduce the pyretic symptoms.

Almost all the drugs that reduce temperature in typhoid fever are antiseptic. All those that are reputed specifics or are generally considered useful are antiseptic: chlorine, iodine, sulphurous acid, the sulphites and hyposulphites, the mercurials, essence of terebinthine, creosote, thymic acid, benzoic acid, salicylic acid, boric acid, iodoform, quinine, resorcin, kairin, antipyrin, thallin. I think, therefore, that experience confirms the general opinion as to their usefulness, and that, practically as well as theoretically, a favorable effect may be obtained in the course of infectious diseases by the employment of the above-named substances. Of these, one especially has been considered a specific, viz.: mercury. It is long since calomel has been administered in large doses, or the black sulphide. Mercurial friction was used by Serres, and by Becquerel, until salivation and ulceration of the mouth were produced. Since that time calomel has been recognized as a valuable agent in Germany and England, and in France by M. Salet, of Saint-Germain. He recommends a method which consists in administering 1 centigram of calomel every hour until salivation ensues. At this juncture the illness takes a turn one way or another.

This mode of treatment being supported by a considerable number of facts, I determined to verify the results. I gave thirty-two patients who were suffering from typhoid fever 40 centigrams of calomel a day, in doses of 2 centigrams every hour, until mercurial salivation was produced.[1] In almost every case this took place in from five to seven days. All the patients that experienced this salivation recovered. The mean duration of the malady was twenty-one days,—a short period, twenty-five days being the usual duration. The mortality was low; two out of thirty-two died, or 6 per cent. Certainly the number of cases was too small to enable us to arrive at any definite conclusions. I may merely mention that those who died were those who had taken the least mercury, and were consequently not sufficiently under its influence. The recoveries in less than twenty-one days were twice more numerous than by the other method.

But I did not continue this treatment, although the patients recovered more quickly, and seemed to recover more completely, as it has the disadvantages of causing a long period of convalescence, great debility, and anæmia. Certain accidents, too, seemed to me more frequent: epistaxis; intestinal hæmorrhage; dysenteric, sanguinolent, and mucous stools. Other patients suffered from later complications,—pneumonia twelve days after recovery from the original malady and a vegetative endocarditis. However, although I rejected this method as an exclusive mode of treatment, I thought it might be used with advantage if the system were less completely impregnated with the drug. I adopted it, therefore, at the commencement of the illness only, and associated it with other therapeutic agents, under the form of a mixed system of treatment, which I shall describe hereafter.

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[1] Forty centigrams equal 6.2 grains; 2 centigrams equal 0.31 grain.

# LECTURE XXII.

## ON THE PATHOGENIC THERAPEUTICS OF TYPHOID FEVER—THE TREATMENT OF HIGH TEMPERATURE.

**The use of calomel in minute doses as a general antiseptic agent.——Consequences of excessive temperature in infectious diseases. The effects of high temperature obtained by experiment. The effects of high temperature as regards denutrition.——Excessive temperature indicates the gravity of the disease, but does not cause it. It is, however, advisable to endeavor to reduce it. Methods of lowering it.——Sources of abnormal heat. Causes of the rise of temperature in febrile maladies.——The effects of antithermic drugs and modes of treatment.**

I HAVE described under four headings the therapeutics of typhoid fever: the general antiseptic treatment, the intestinal antiseptic treatment, the antipyretic medicinal treatment, and the dietetics of food and drink.

I have described at some length, in speaking of chronic intoxications of intestinal origin, how I proceed with the intestinal antiseptic treatment; in my last lecture I gave my reasons for rejecting the general antiseptic treatment by the exclusive use of mercurial salts, at the same time admitting the specific action of mercury. Thus, I employ part of the general antiseptic method in combination with other modes of treatment.

I use calomel in minute doses at the outset, and until the commencement of the second week. I administer each day 40 centigrams of calomel, divided into 20 doses, which are taken every hour, without either trying to produce or obtaining salivation. This treatment is continued for four consecutive days. Generally speaking, it has seemed to me that the thermic curve was modified, and that sometimes after the second day the fever began to abate, varying, at the end of four days, between 39° C. (102.2° F.) and 40° C. (104° F.), at a period when in the ordinary course of the malady the temperature would either be rising or remaining stationary. I do not wish to produce and I never obtain salivation.

I will now proceed to discuss those antipyretic or antithermic drugs that are in great favor at the present day. There is a certain school of medicine that sees nothing in fevers but fever; with doctors of this class the thermometer is the source of all therapeutic and prognostic indications; they see improvement only in lowering of the temperature. No clinical practitioner can accept such a doctrine, and the audacity of the assertions of the school in question has given rise to a reaction in the contrary direction, in Germany as well as in France. Thus we now see the current of medical opinion take a new course. It is now urged that fever may do some good, and that it should be treated with respect,—a theory that has long been unheard of in the medical world. This is a return to the Hippocratic and traditional doctrine, which I have supported as regards diseases of nutrition.

I have dwelt upon the theory that there are fevers which, at certain times, re-establish equilibrium in exhausted nutrition by bringing about interstitial metamorphoses. This is evident in gout. But is it also true of infectious diseases? Can fever help the system to free itself from the infectious organism? We know that certain microbes cannot live beyond certain temperatures which do not kill a human being. The bacteria of malignant pustule, which cannot live in a temperature higher than 40° C. (104° F.), have no effect on birds, their normal temperature being above that point. Pasteur has shown that it is necessary to cool a fowl, in order to render it able to contract this disease. This experimental argument is brought forward to show that the elevation of the temperature of the body in fever creates a physical medium that is unfavorable to the infectious organism.

Nevertheless, the whole school of which I have already spoken sees in pyretic maladies no other danger than that which results from elevation of temperature. Liebermeister says expressly that the danger in fevers lies, above all, in excessive elevation of temperature. He brings forward as an argument the coagulation and decomposition, at 44° C. (111.2° F.), of the lecithin which enters into the composition of the nervous elements and of the corpuscles of the blood. At 42° C. (107.6° F.), at 43° C. (109.4° F.), and even at 41° C. (105.8° F.), the nerve cells show abnormal excitability in the animal experimented upon. We note muscular agitation and acceleration in the beating of the heart and of the respiratory movements. The phenomena of osmosis are modified by elevation of the temperature. Water is retained in the cells. The tissues of those suffering from fever are richer in water than when they are in their normal state. All this is, unfortunately, true. But these are not the only phenomena to be considered in cases of fever, and, moreover, the elevation of temperature in illness does not reach 44° C. (111.2° F.), or even 43° C. (109.4° F.), unless it is, exceptionally, at the moment of death or a little while after it.

Naunyn and Rosenthal have studied the effects of excessive elevation of temperature obtained artificially. At 44° C. (111.2° F.), the cardiac muscle, like the other striated muscles, remains contracted, and death ensues; but the same experimenters were able to keep rabbits alive for weeks ranging between 41° C. (105.8° F.) and 43° C. (109.4° F.), without any ill effects being observed.

It is the same with fatty degeneration of the viscera, which I studied in 1867, making experiments in elevation of temperature upon a dog. I caused the animal to raise its temperature itself, simply by preventing it from losing the greater part of its heat. It lived in an atmosphere saturated with moisture, and heated to a degree very little below its own temperature. Thus the loss of caloric, by contact and by evaporation, was suppressed; the animal, continuing to produce heat, accumulated it. The effects thus obtained by the gradual elevation of temperature are increased action of the heart (300 beats) and of respiration (80 to 90). The animal died, at 44° C. (111.2° F.), at the end of about four hours. Independently of hæmorrhages under the pleura and the pericardium, we observed, four hours after the commencement of the elevation of temperature, fatty degeneration of the cardiac muscle and of the hepatic cells. I was led to think that the excessive elevation of temperature was the cause of the fatty degeneration, but Naunyn and Rosenthal found that no similar effect was produced in animals at the excessive temperatures observed in man when suffering from disease.

On the other hand, elevation of temperature does not seem to increase nutritive metamorphoses; the waste of nitrogenous tissue is much the same when animals are subjected to elevation of temperature as when they are in a normal condition (Simanowsky). Speaking from a clinical point of view, there is in a patient no parallel, notwithstanding the assertions of Hirtz, between the excretions of urea and the elevation of temperature. It cannot be said that high temperature appreciably increases disassimilation. Charvot had already been struck, when he was studying the elimination of urea in typhoid fever, at the slight elimination that took place during the hyperthermic period, whereas it increased during the abatement of the disease, and still more during the period of convalescence. I pursued this question further, studying the variations in the weight of the body in typhoid cases. In these cases all the combustions supposed to be necessary for the production of excessive elevation of temperature are compensated for, the diminution in weight being quite insignificant, whereas, when they enter upon convalescence, the diminution in weight is rapid, and attains its maximum after apyrexia, when food is administered to the patients. Excessive elevation of temperature is, therefore, not a source of danger from the point of view of anatomical lesions or from the point of view of denutrition. We may say, therefore, that it indicates the gravity of the disease, but does not cause it. Elevation of temperature announces, but does not constitute, the danger. It is even an established fact that the accelerated action of the heart which accompanies elevation of temperature cannot produce exhaustion of the heart; the functional incapability through excess of work is a myth, for the mechanical work effected by the heart is less when the contractions are so rapid (200 to 300 pulsations). The relaxation of the capillaries and the diminution of the arterial and venous tension relieve the heart, and, from the point of view of fatigue, the lessening of the resistance is not counterbalanced by the multiplication of the cardiac contractions.

However, these considerations do not alter the fact that methods of lowering the temperature are useful in certain cases, or that when we have succeeded in lowering the temperature we note an improvement in the symptoms and an amelioration in the general condition of the patient. Although the complications experienced by a patient whose temperature is 40° C. (104° F.) or 41° C. (105.8° F.) do not seem to result from the elevation of temperature, nevertheless drugs or modes of treatment that lower this excessive temperature cause some of these complications to disappear. This is seen to be the case, at least, with typhoid fever and certain cases of scarlatina or cerebral rheumatism, for, except in these three diseases, it is not certain that antipyretic treatment is really useful. How, then, shall we deal with excessive elevation of temperature? By acting upon the causes which produce normal heat or abnormal heat? We cannot choose indiscriminately between these two methods. We may reduce the sources of normal temperature by bleeding, by abstractions of serum, or by the administration of poisons producing the same effect (veratrine and tartrate of antimony). These methods, long in use, are now almost entirely abandoned.

But what are the sources of abnormal heat? We do not know yet, we can only surmise. They must be very different according to different diseases. Are they normal processes carried to excess, or are they abnormal processes that raise the temperature to fever height? It has been suggested that there are microbes which burn side by side with normal organisms and raise the temperature in the body as in test-tubes. This is merely a hypothesis, supported by analogies, but not by experiment.

Another hypothesis is that of the retention of heat. It has been said that tissue wastes more quickly in fevers. This is true in certain diseases; in acute atrophy of the liver, for instance; but it is not true in typhoid fever. Chalvet, twenty years ago, observed, after Traube, that in a fever patient the heat radiation is less than in a healthy person. A square decimeter of his skin loses a smaller number of calories than a square decimeter of the skin of a person in normal health. It is possible that a diminution in the abstraction of calorie results from this.

The rapid diminution of the corpuscles of blood in febrile diseases has been brought forward as showing a more rapid destruction of matter. Bockmann replies that, the moment the temperature becomes normal again, the corpuscles suddenly reappear. They remain suspended in some part of the body during the fever. Bockmann and Naunyn admit that they are temporarily withdrawn from the general circulation. This would account for the great increase in volume of the spleen. Hüter has observed, in septic and pyæmic disorders, stagnation of corpuscles in certain parts of the capillary blood-vessels; this fact may be mentioned as corroborating the theory of a temporary abstraction of some of the corpuscles.

Winternitz has quite recently revived the opinion that the retention of heat is the cause of fever. Marey also attributed fever to a defective distribution of caloric. If, therefore, certain fevers may be caused by the retention of heat, it may be suggested that the radiation of the latter should be increased. Riess, experimenting upon animals suffering from infectious diseases, lowers their temperatures artificially until they become normal; but the diseases continue and death ensues. The danger, therefore, does not lie wholly in the excessive elevation of temperature.

Nevertheless, I repeat that clinical experience shows that the antipyretic treatment is advantageous. How then does it act? Let us endeavor, as far as possible, to know what we are doing when we employ antithermic agents; those that have been used successfully are quinine, salicylic acid, antipyrin, kairin, thallin, and, above all, hydrotherapeutic treatment.

Murri has succeeded in showing that all these methods raise the temperature of the skin, and, consequently, bring the heat to the surface of the body, thus favoring the lowering of the central temperature. Moreover, they do not act upon a fever patient in the same way as upon a person in health. Quinine does not lower normal temperature; yet it can, in typhoid fever, cause the temperature to fall three degrees in a few hours. In a healthy person it raises it one- or two- tenths of a degree, but it increases the flow of blood to the skin. This is true in a higher degree of salicylic acid, which favors perspiration; like the cold-bath treatment, which at first physically abstracts a few degrees of heat, but afterward favors the relaxation of the cutaneous capillaries, the congestion and heating of the skin; then the cooling, at the surface of the body, of a larger quantity of blood from the central organs.

Theoretically, the cold-bath treatment increases combustion, and should therefore increase calorification; this is true in the case of a healthy man, who then produces more heat than unde normal conditions. But in the fever patient this treatmen retards calorification. In typhoid fever, according to Sassetzky the patient does not give off more carbonic acid and does no excrete more urea when he is subjected to refrigeration. Takin into account the uncertainties of theory, we are justified in concluding that the causes of fever are various; that it depend sometimes on an increase of the normal calorification, sometimes on the life of infectious organisms, and sometimes o the retention of the normal heat. In any case we may safely sa that the antithermic method is not without its uses in typhoi fever; that in this disease quinine is useful; that it answers t certain indications and realizes certain effects; that it is th same with cold baths; but that in other disorders—pneumonia, pleurisy, etc.—this antipyretic treatment does not offer the sam advantages.

# LECTURE XXIII.

## PATHOGENIC THERAPEUTICS OF TYPHOID FEVER—NEW MODE OF BATHING IN FEVERS; DIETING OF FEVER PATIENTS.

Uncertainties regarding the nature of fever. Probable multiplicity of the pathogenic sources of fever. Impossibility of counteracting it by pathogenic therapeutics. Antipyretic modes of treatment acquired by empiricism. Antithermic drugs. Inconvenience of phenic acid and antipyrin. Utility of quinine. My method of administering quinine in typhoid fever.——Hydrotherapeutic modes of treatment: lotions, wrappings, baths. The methods of Brand, Liebermeister, Ziemssen, Riess. Their advantages and disadvantages. My method: tepid baths, gradually cooled, but remaining tepid. Details of their administration. Their advantages.——The dieting of patients in typhoid fever and other long fevers.——Didactic summary of my treatment of typhoid fever. Statistical results.

BEFORE entering upon the practical side of the antipyretic method, it would be expected that we should discuss the doctrines concerning the nature of fever. But, in examining pyretological doctrines, we are met at every point by contradictions, and I see that I am reduced to the confession, so humiliating to a professor of general pathology, that I do not know what fever is.

Galen was not troubled with these uncertainties. To him *febris* was *calor præter naturam*. This is a definite and concise assertion, and the *résumé*, as it were, of a description of the morbid state. But now science demands further particulars, and wishes to know the origin of this morbid condition, and what is the source of fever.

It is not certain that there is *one* pathogenic source of fever. I think, myself, there are several pyretogenetic processes. We may raise the temperature of a body in various ways, by combustion, radiation, friction, condensation, etc.; in the same way the temperature of the bodies of animals may be raised abnormally under very varying conditions.

Fever may be the result of an increased combustion or an increased dehydration, or it may be produced by the liberation of the heat produced by the life of infectious germs, or by a diminution in the losses of the body, or by resolution of the forces of tension.

In the living organism forces exist that are developed by the metamorphosis of the matter in the cells, and which do not act externally, either by motion or by heat. Life is a sort of unstable equilibrium that is maintained by the forces of tension. These oppose the freedom of the chemical and physical actions, where opposite electrical actions meet, the acids and alkalies. J. Ranke proved, long ago, that the nucleus of a living cell is electro-positive, whereas its envelope is electro-negative. Why do not these opposing kinds of electricity combine to bring about a condition of electrical neutrality, unless it is because they are prevented by the opposing forces of tension? If death occur, neutralization is immediate.

It is the same with the nerves as regards the electrical condition of the axis-cylinder and of the envelope; the former is acid, the latter alkaline, during life; upon death, neutralization ensues. The combustion being the same, if the tension is diminished, part of the force will become apparent under the form of heat. Is this theory regarding fever applicable to certain forms of pyrexia? I do not know. We can only form hypotheses on this subject. Remember what I said about uræmia. We have found poisons, but not the poison of uræmia. As regards fever, there may exist not one single explanation, but various pathogenic conditions. I have, moreover, called attention only to those processes for which experimental or clinical data can be furnished.

In short, fever is with us as with Galen,—elevation of temperature arising from causes that may strangely vary. Now, from a therapeutic point of view, not being sure what fever is, we are compelled to give up the idea of drawing up a system of pathogenic therapeutics for its treatment.

We are thus obliged to return to empiricism, which is not sufficient to satisfy us, but which can give us information resulting from the long accumulation of individual facts. Let us, therefore, enter the domain of empirical observations.

We know, empirically, that certain modes of treatment lower the temperature and bring about an improved state of affairs. Thus, in the first place, quinine has evidently a beneficial action on typhoid fever and some other forms of pyrexia, intermittent fever, and in one form of infection of women in childbed its action is undoubtedly favorable, although only temporarily.

Phenic acid has a certain antipyretic action, but perhaps not a favorable one; antipyrin has also this action, but its influence is unfavorable. When the temperature is at 40°[1] or 41° C., a sufficient dose of quinine produces a fall of from 1 to 3 degrees, which may last for twenty-four hours. At the same time we note also the disappearance or diminution of the nervous troubles that were attendant upon the high temperature; the patient is evidently better, and accidents which might soon cause death may thus be averted. It would, therefore, on first thoughts, seem advisable to prolong indefinitely this favorable effect. Vogt twenty years ago, and Joffroy recently at the Hôtel-Dieu, have tried the continuous administration of quinine. I also wished to see what results could be obtained by this means. I was soon obliged to abandon the experiment. With 2 grams of quinine we get a fall of 1, 2, or 3 degrees; but in the evening of the next day the temperature rises again, and by the morning of the following day the fever has reached its original height. Should quinine, therefore, be administered in the evening as a preventive? The second dose, moreover, does not produce the same effects. Three days at least must elapse before the quinine regains its power. It is an intermittent remedy. It has been asserted that if given continuously the temperature varies between 39° and 40° C., instead of between 40° and 41° C. Is this advantage sufficient? As for myself, I never give a second dose of quinine until after an interval of seventy-two hours. I only give it then if the temperature taken in the morning in the rectum exceeds 40° C., or if that taken in the evening exceeds 41° C. The doses that I have adopted are 2 grams during the first and second periods of seven days; 1 $^1/_2$ grams in the third period; 1 gram in the fourth and after. I never give less than this; $^1/_2$ gram would be of no use. It is well to know that from the eighth to the eleventh day we often obtain only a slight lowering with doses that are generally efficacious either before that time or after. This is almost necessarily the effect produced by quinine; it aims only at an accident, viz.: the excessive elevation of temperature.

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[1] Forty degrees C. equal 104° F. To convert Centigrade degrees into Fahrenheit multiply by 9, divide by 5, and add 32 to the result.

As for other remedies that are reputed to be antithermic,—phenic acid, resorcin, antipyrin, thallin,—you cannot depend upon them. In regard to antipyrin, the lowering that it produces is rarely accompanied by an improved general condition, for it causes at the same time a lowering of nervous activity. The only objection to quinine, setting aside the buzzing in the ears, which, however, affects fever patients less than persons in health, is the accusation urged against it that it is liable to cause sudden death. During ten years, out of five hundred cases, I have only found sudden death occur seven times with patients who were taking quinine. Four of these deaths happened in the same week; and in several hospitals, at the same time, similar cases came under my notice. But chemical analysis showed that the drug administered to the patient under the name of quinine was really not quinine. It was a compound little known, in which cinchonine predominated. If we set aside these cases, therefore, there remains three cases of sudden death out of five hundred cases of typhoid fever,—a proportion which does not exceed the ordinary percentage of sudden death in this malady. The postmortem examination showed that in the patients that had died suddenly the heart was contracted and absolutely empty of blood. Now, the toxicology of quinine teaches us that when death is caused by this drug the heart is found to be dilated and gorged with blood. Moreover, since that time, I have not had a case of sudden death.

In short, then, I consider that by administering quinine to typhoid patients, according to the rules already stated, we obtain, as well as a diminution of temperature, an improved condition generally. But I must add that in most other forms of pyrexia this treatment has failed. In pneumonia, pleurisy, and erysipelas, we obtain, as a rule, neither a fall of temperature nor an improved general condition.

Abstraction of heat is the only nonmedicinal means of lowering the temperature of fever patients. Many methods of abstracting heat in fever patients have been tried. Since the time of Sydenham and Currie, cold air has been used, currents of air between open windows, and cold water in various ways.

The continuous sprinkling of the patient is, perhaps, the most painful process. A cold shower bath also produces a disagreeable nervous action. Bathing with cold water gives an unpleasant shock, and the abstraction of heat by these two methods is very slight. Wrapping in a wet sheet is painful for some moments.

Local applications, such as a bladder of ice on the abdomen, produce, at first, a vascular spasm, and then stasis in the vessels; the skin is chilled and the cellular tissue also; necrosis may set in, but the body, as a whole, is not cooled.

The circulation of cold water by means of the ingenious contrivances of Dumontpallier and Clement produce a real refrigeration, but these processes are little used as yet, and I am not, therefore, in a position to express an opinion as to their merit.

Enemata of cold or iced water certainly cool the rectum, but they do not produce a general reduction of temperature.

It now remains for us to speak of the method which is generally preferred,—the ordinary bath, in which the temperature of the water is lower than that of the body of the patient.

The cold bath may be given according to the method of Brand or Liebermeister. According to Brand, when the temperature exceeds 38.5° C., a bath of low temperature is given eight times a day, for from ten to fifteen minutes.

Liebermeister leaves the patient in the bath throughout the whole course of the illness; the duration is the same, and he gives twelve baths a day. The temperature may be 15° C., but this has been abandoned; from 18° to 20° C. is the general rule; it may be even 25° C. Care must be taken to apply cold water to the head first.

The patient is left in the bath until the cold chill is complete, and he is often taken out in an alarming state. Our feelings must be well under control if we are to carry out this treatment rigorously in face of the sufferings of the patients. It is worth mentioning that if we cause them great suffering we can almost guarantee their recovery. But is there no treatment that is as efficacious without being so inhuman?

The cruelty of cold baths has led to tepid baths being substituted for them. There is the tepid bath at a disagreeably low temperature, viz.: 28° C., which might as well be called a cold bath; for to a man whose temperature is 40° C. the sensation is the same at 28° C. as at 25° or 20° C.

Ziemssen has proposed a tepid bath, gradually cooled. The temperature, at first, is 35° C., and to a fever patient even this gives a very unpleasant sensation of cold. Then the temperature of the bath is rapidly lowered, so that in ten minutes it falls to 25° C. The patient remains in this cold bath for from ten to fifteen minutes, until the teeth begin to chatter, as in the methods of Brand and Liebermeister. This is the cold bath preceded by a short phase of bearable temperature. But this method does not do away with the sudden nervous shock.

I will also mention Riess's continuous bath, which lasts twenty-four hours a day at a temperature of 34° C. The temperature is moderated by this method, which may be useful. The mortality would be 6 per cent., according to Riess, but his statistics are only derived from forty-eight cases. This continuous tepid bath becomes rapidly unbearable, and the patients prefer the cold baths according to Brand's method.

I will now describe my own method, which I have been trying for more than a year. My object was to develop a bath in which the patient might lose heat without any nervous shock or spasm of the cutaneous vessels. What we wish to arrive at is not merely abstraction of heat by contiguity or conductivity. On the contrary, what we require is that the blood should come from the center of the body to the surface to be cooled.

The temperature of the bath, at first, is two degrees below the central temperature: 38° C., for instance, if the temperature of the patient is 40° C. The patient can bear this well and experiences no shock. The water is gradually cooled at the rate of one-tenth degree per minute, or one degree in ten minutes, until it is lowered to 30° C., but it is never cooled beyond this point. The time necessary for this cooling is an hour and a half if the temperature of the patient is 40° C., or an hour and ten minutes if it is 38° C.

No feeling of nervous shock and no peripheral vascular spasm occur during this long period. The pulse is not constricted. At about 33° C. the patient finds his bath cool; at

32° C. he finds it cold, but even at 30° C. he continues to speak and talk, showing a wonderful mental condition. He has nothing of the typhus stupor about him. The lowering of temperature realized is much more considerable than with the cold bath.

I give the bath eight times a day, like Brand. Certain patients can thus pass half the day in the water. The lowering of the temperature is more lasting than with the cold bath, and sudden rise of temperature is much less considerable.

By plunging a patient into a bath which is only two degrees below his own temperature, I do not provoke the reflex vascular spasm that prevents the blood from coming to the skin to be cooled. The lowering of the temperature of the water is effected insensibly, and never transforms the bath into a cold one.

What are the effects that result from baths administered according to the mode that I recommend? An almost constant lowering of the central temperature, a refrigeration which varies according to the stage of the disease and the hour of the day. The cooling is, on an average, five-tenths of a degree; it may sometimes amount to three degrees. I speak from an experience supported by the results of six thousand baths. Some exceptions should be mentioned. For instance, in certain patients the temperature is not reduced; we even observe a rise of temperature of one- to five-tenths of a degree. This anomaly is seen in certain very nervous women, and in certain men toward the end of the treatment, when the repetition of the baths has ended by developing in them an insurmountable repugnance and keen irritation.

The elevation of temperature which takes place after the bath is slow; it is never a sudden rise.

It is to be remarked that we succeed better in cooling the patient in proportion as his temperature is higher, so long as his temperature remains between 37° and 40° C.; but, on the contrary, with patients whose temperature is excessive, above 40° and 41° C., the cooling is slighter in proportion as the temperature is higher. The lowering is less between 41° and 42° C. than between 40° and 41° C. Below 38° C., also, cooling is difficult; a man in health is scarcely cooled at all in a tepid bath.

The differences in the lowering of the temperature in the baths vary also according to the periods of the disease. In that stage where excessive temperature is the leading feature, and at the commencement, it is more difficult to cool the patients; the average fall is five-tenths; later on it is six-tenths; and in the fourth week, seven-tenths.

There are also variations according to the time of day. The temperature of a typhoid patient rises from 7 o'clock in the morning to 3 o'clock in the afternoon; then a diminution takes place, and after that another rise, the maximum of which is reached about midnight. From midnight to 7 o'clock it abates again, and the patient loses the excess of temperature that he had gained during the day. It is between midnight and 6 o'clock in the morning that the most important diminutions of temperature are obtained after the bath; a fall of three degrees is often observed toward morning.

Do the patients derive any other benefits from the baths besides the physical abstraction of heat? Without doubt they do. In the first place the lowering of temperature resulting from the bath is accompanied by an improved general condition, as with quinine; whereas with the diminution of heat obtained by means of antipyrin the general condition remains the same or grows worse.

Other advantages also are obtained. When delirium sets in at the commencement, it abates after, at the most, three days of the treatment. There is no more of the real typhus stupor. The patients that are treated by the baths do not cease to understand what is said to them and to answer questions.

According to Skinner, one of my pupils who has written a very good thesis on the study of my system of baths, we find that the patients always take great interest in the variations of their temperature, and discuss among themselves during the bath the number of tenths of a degree noted before and after.

The tongue remains moist, and if dry at the beginning of the treatment, this dryness disappears after a few baths. The teeth are not discolored. The complexion has not that earthy pallor that denotes the thorough poisoning of the system. It is white and often even pink in those patients that have a fine skin.

Last, the need of sleep manifests itself after each bath, and the patients enjoy sleep at night,—an unusual thing with typhoid patients. For this last reason I do not give baths from 2 to 6 o'clock in the morning, for fear of disturbing this night-sleep, which is precious. Only in order to give the eight baths in the twenty-four hours, the intervals between them should be a little shorter from 3 o'clock to midnight. Speaking of the advantages of baths I may mention the rarity of eschars.

But all these results are obtained from tepid baths in typhoid fever only. We have said that cold baths could be employed in pneumonia, erysipelas, and pleurisy. I tried in these diseases cold baths and tepid baths systematically cooled. I did not in these cases observe the salutary effects which are so evident in typhoid fever.

Thus I do not think that this can be called a general antithermic method. Perhaps, however, it would be applicable to certain hyperthermic forms of scarlatina and cerebral rheumatism. I cannot speak from personal experience on this point. I have, however, observed remarkable results from it in measles.

Are there no disadvantages attendant upon this system of tepid baths gradually cooled?

We cannot attribute to them pulmonary congestion, which is neither more frequent nor more marked than with other modes of treatment, and which, on the contrary, very often decreases during the baths. Neither pneumonia, pleurisy, nor any other grave visceral lesion has been reported as resulting from the baths. But when the epidermis at last becomes puffy and macerated at the palms of the hands and the soles of the feet, we often find, in the case of workmen, or in cases where the epidermis is very thick, that whitlows and accumulations of pus close to the nails form under the skin. Besides this inflammatory complication, it is not unusual to find, after a few baths, a rather painful glandular swelling in the axilla, but never real adenitis. The hands and feet must be watched so as to let out the pus as soon as it is observed, or we shall find that extensive inflammation of the lymphatics will soon ensue. However, these are accidents of minor importance.

I discontinue the use of the baths in the event of intestinal hæmorrhage or pulmonary hepatization. When, in a female patient, the menstrual period occurs during the course of typhoid fever, I do not generally find it necessary to interrupt the baths.

I now come to an important point in the therapeutics of grave pyretic diseases,—the question of diet.

In these disorders, and especially in typhoid fever, the secretions of the digestive tube are dried up or perverted. It seems, therefore, *a priori* impossible to feed the patients, and natural to condemn all attempts at alimentation.

Milk, which is so easy to digest, and which from its fatty nature and its sugar seems so well adapted to keep up the strength of fever patients, and to make up for the waste caused by combustion, is not without its drawbacks. It raises the temperature, and the urinary secretion is lessened. Those who are in favor of a milk regimen order a large quantity to be given in typhoid fever so as to increase the urinary secretion. Now, when I give milk in any considerable quantity, I notice that it causes, through indigestion, an aggravation of the patient's condition. I therefore maintain that all food should be rigorously withheld. But I give water in abundance, and water containing substances that are slightly nutritive and capable of introducing into the system certain mineral elements, under the form of meat extract, broth, and cereal extract. This latter was considered useful in fever cases two thousand years ago. The *ptisan* of Hippocrates was a decoction of barley; strained ptisan was prescribed at the beginning of fevers, and ptisan that was not strained at the end. I give my patients an extract of meat and barley which contains mineral elements that are calculated to repair the losses resulting from the disassimilation of mineral material in the cells. I endeavor to prevent the waste of mineral matter, as it plays the part of middle-man in organic changes. Chloride of sodium is indispensable for the phenomena of osmosis; phosphates are the media between the bases and the acids.

To this regimen I add vegetable acids, in the form of lemon-juice, which introduces potass, and which is combustible.

Last, I administer substances that are both plastic and combustible,—peptones. I give 50 grams[1] per day, reckoning the dry peptone. These peptones, which are chemically pure and prepared properly, and which are very different from certain products sold under the same name in commerce, are, as we have said, plastic combustible substances calculated to make up for the waste of nitrogenous matter in the body.

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[1] *I.e.*, a little more than 1 $^1/_2$ ounces of dry peptone.

In the regimen of our typhoid patient another substance that figures as a combustible agent is fat in a form that can be absorbed,—*i.e.*, glycerin formed outside of the system, for we know that glycerin is one of the products of the division of fatty substances in the duodenum. The patient absorbs every day 200 grams of glycerin, and yet is not purged. I only allow wine in very small quantities.

This is the whole of my system of dietetics. Thanks to it, only a very slight loss of weight is observed during the period of fever. The loss of weight is sometimes *nil;* it varies generally between 100 and 300 grams a day up to the end of this period, as far as the fifteenth day; later on, at the moment of the crisis, and when convalescence is established, the loss may amount to 1 kilogram per day for from three to five days; but, from the third day after alimentation is resumed, the weight of the patient increases again. Several principles of this dietary are applicable to the intense fever of certain chronic maladies. In the acute pyrexia of very short duration, as in pneumonia, the necessity for alimentation is not so urgent.

I will now sum up briefly and didactically the rules for the treatment of typhoid fever as I have just described it. These rules may be classed under four main headings: the general antiseptic treatment, the intestinal antiseptic treatment, the antithermic treatment, and the regimen to be observed.

As soon as the diagnosis is made or suspected, I prescribe:—

*(a)* A purgative, to be repeated regularly every three days (15 grams of sulphate of magnesia).

*(b)* Forty centigrams[1] of calomel per day, in 20 doses of 2 centigrams (one every hour), are administered for four consecutive days. This constitutes the general antiseptic treatment.

*(c)* The intestinal antiseptic treatment consists in mixing 100 grams of powdered vegetable charcoal with 1 gram of iodoform and 5 grams of naphthalin. The whole is mixed with 200

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[1] Forty centigrams equal 6.2 grains.

grams of glycerin and with the 50 grams of peptone that form the basis of nourishment. This mixture forms a black, semi-liquid paste, which is taken in twenty-four hours in doses of a tablespoonful every two hours in a third of a glass of water. I wash out the bowels regularly every morning and evening by means of an injection containing 1 part in 1000 of phenic acid, each injection consisting of 50 centigrams of phenic acid to 500 grams of water.

*(d)* From the first day the patient takes eight baths a day until he is completely cured, when the temperature varies between 37° and 38° C. The baths are resumed if the temperature exceed 37.5° C. I reserve quinine for cases in which, notwithstanding the baths, the temperature remains too high. The doses are 2 grams during the first two periods of seven days, 1 $^1/_2$ grams during the third period, and 1 gram during the fourth and fifth. These quantities are administered in large doses—50 centigrams—every half-hour. But I do not return to quinine until after an interval of three days. The signal for the employment of quinine is a temperature in the rectum of 40° C. in the morning or 41° C. in the evening. Often the baths dispense with the use of quinine and constitute in themselves a sufficient system of antithermic treatment.

*(e)* The diet comprises: broth cooked with barley and administered freely (1 $^1/_2$ liters to 2 liters a day); glycerin (associated, as I have said, with charcoal, iodoform, and naphthalin, and also with peptones); lemonade made from lemons, with the addition of a little wine.

This is certainly a complicated system of therapeutics; it cannot be otherwise, as the indications to be fulfilled are complex.

This systematic treatment, be it understood, does not exclude the treatment of certain accidents; for instance, excessive or prolonged delirium by opium, peritonitic complications by means of ice or Neapolitan ointment. I have only discussed those symptoms that are common to all patients; for if, as has been said, we are to study the patients and not the disease, it is no less true that all patients show in their illness general features without which they would not have the disease at all. Why should I be reproached for employing a systematic mode of treatment? Is it not as natural to contend systematically with excessive temperature, infection, and self-poisoning, as it is to feed one's self systematically every day? When I discontinued the baths for some reason in the course of the illness, the temperature in the patients went up again to 40° and 41° C., and sometimes they died.

What results have I obtained from my method?

Formerly the mortality from typhoid fever, in the cases that came under my notice, was 25 per cent. When I succeeded in neutralizing the intestinal poisons, it fell to 15 per cent., then to 10 per cent., when I obtained a successful intestinal antiseptic treatment. It has fallen to 7 per cent. since I instituted the complete system of treatment, which was in April, 1884.

This is a better result than Liebermeister has obtained by cold baths. And I reckon the total mortality, including patients that arrive at the hospital at a very advanced stage of the fever, without having been treated at all, having, as I found in one case, a temperature of 42.6° C., and those who are brought to us already attacked with peritonitis through perforation; I include deaths that may be attributed to later complications, cases in which the treatment has been suddenly discontinued for some cause or other, and those cases in which the method has not been strictly carried out. Thus, in the beginning, when it was not possible for me to arrange for baths at night, in the case of one patient, the temperature, which had fallen during the day under the influence of the baths, rose in the night to 42° C., and the third night he died.

The number of patients that have been subjected to the complete treatment is now one hundred and twenty-nine,[1] out of which there have been nine deaths, showing a mortality of 7 per cent. The mean duration of the illness has been nineteen days. The frequent relapses which attack 20 per cent. of the patients have fallen to 10 per cent. in the last period. In fact, we have every reason to congratulate ourselves on these results; and I am convinced that we have obtained them by attacking the malady wherever we find it vulnerable, in its primordial cause—infection, as in its necessary effects—poisoning, fever, and inanition.

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[1] At the date of this publication (November, 1886) the number of cases of typhoid fever treated by M. Bouchard's staff at the Lariboisière Hospital since April 1, 1884, is 226, out of which there have been 31 deaths, or a mortality of 11.7 per cent. Is this increased rate of mortality to be attributed to a chance accumulation of critical cases, or to a modification introduced into the treatment, salicylate of bis-

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muth having been substituted for the charcoal, and the peptones having been suppressed against his will, during a considerable period? But in any case 11.7 per cent. is low as compared with the general mortality in this hospital. The Lariboisière Hospital has been open a third of a century, and during that time the average mortality in typhoid fever has been 21 per cent. It is still 18 per cent. for the last six years.

# LECTURE XXIV.

## AUTO-INTOXICATION BY BILE. PATHOGENESIS OF JAUNDICE.

The elements constituting bile. Experimental studies of the toxic nature of bilirubin and the biliary salts. How the greater number of the elements of bile become inert by precipitation in the digestive tube. The rôle of the liver as a protecting agent against the part that might be reabsorbed. When bile passes into the blood, the white connective tissues, by fixing the bilirubin, prevent it from injuring the other elements. The urine then draws it off little by little. The biliary salts are gradually eliminated by the urine. The sudden injection of a considerable quantity of bile into the blood kills animals without producing jaundice. The slow injection of the same quantity of bile causes jaundice and does not kill. Influence of biliary retention on the hepatic cells and on nutrition.

BEFORE concluding the study of intoxication by the natural poisons of the system, I will discuss poisoning by bile, or jaundice. This is a question that I have already touched upon incidentally when, in speaking of uræmia, I had occasion to quote some of the data relating to the poisonous nature of bile. When once it is spread over the surface of the intestines, bile is found to be under very different conditions than when it is in the liver. The reabsorption of bile takes place, no doubt, with some intensity in the duodenum, but it is principally inoffensive matter that is reabsorbed, and, moreover, if the noxious portion of the bile is reabsorbed in any considerable quantity, it is again stopped by the liver and rejected into the intestines. In order, therefore, to study fully the toxic effects of bile we must examine it in the liver at the moment of its secretion.

Bile is very abundant, being almost equal in quantity to the urine; its secretion is over 800 cubic centimeters in twenty-four hours; and it may even amount to 1200 and 1300 cubic centimeters. It is a diffusible liquid, passing by means of exosmosis into the blood; it is rich in solid substances (from 10 to 15 per cent.) all capable of dialysis. Bile does not contain albumin; but mucin is found in it, and this gives to it its viscosity; it also contains cholesterin, which is erroneously considered poisonous, as we find considerable quantities in atheromatous abscesses of the aorta; olein, margarin; coloring matter,—important from a toxic point of view; the biliary salts and the alkaline soaps, by means of which ingredients the cholesterin is held in solution.

Of the various coloring substances, bilirubin is the only one that we need discuss; the others—bilifulvin, biliverdin, bilifuscin, biliprasin, and bilihumin—are merely derivatives of bilirubin. Bilirubin is soluble in water and in chloroform; it gives rise to Gmelin's reaction when treated with nitric acid. This coloring matter is generally precipitated suddenly in the intestines, on contact with the acid chyme, which renders it insoluble and prevents it from being reabsorbed. We must take into account the biliary salts whose base is sodium, which is a nonpoisonous base. The glycocholic and taurocholic acids of Lehmann, still known as cholic and choleic acids, are very unstable. Under the influence of potass and heat they generate cholalic acid, and, besides this, the first named gives off glycocol, and the second taurin. The biliary acids are also transformed, under the influence of sulphuric acid, into choloidic acid and into glycocol or taurin,—a reaction which, upon contact with certain digestive juices, is effected in the intestines as in the test-tube. Finally, the cholalic and choloidic acids take the form, in the intestines, of an insoluble substance, viz.: dyslysin, which is no longer injurious.

The coloring matter and the biliary acids, which are both poisonous, becoming thus insoluble in the intestines, we need not wonder that, notwithstanding the quantity of bile poured into the intestines and the intensity of its reabsorption, no poisoning takes place, even when the kidney is only slightly permeable. But these transformations are neither immediate nor constant. In certain persons we find, even near the anus, bilirubin still intact, and biliary acids that have not undergone transformation, owing to the rapidity and intensity of the contractions of the intestines.

Even in a normal state of health a certain quantity of the toxic matter may be reabsorbed in the duodenum. But the liver, as Schiff has shown, arrests these poisonous substances and restores them to the intestines or transforms them into harmless matter.

In any case, the reality of the toxic nature of bile, which has long been believed in by the medical world, has recently been experimentally established. According to my experiments, from 4 to 6 cubic centimeters of bile are required to kill in convulsions a living animal weighing 1 kilogram, and, since the daily secretion of bile is about 1000 cubic centimeters, we must conclude that during every twenty-four hours a man makes, by the activity of his liver alone, an enormous quantity of poison,—enough to kill, in twenty-four hours, three men of his own weight, 1 kilogram producing enough to kill more than 2800 grams of living matter. Man forms, in eight hours, enough poison to kill himself simply by his hepatic secretion. Now, in twenty-four hours the urine does not eliminate half the quantity necessary to poison a man; the urine of two days and four hours would be required in order to do this. The volume being equal, bile is nine times as poisonous as urine; in an equal period of time the biliary secretion represents a degree of toxic power six times as great as the urinary secretion. I have shown that bile decolored by carbon has one-third of the toxic properties of bile in its natural condition.

This leads us to suspect the toxic nature of bilirubin. We—M. Tapret and myself—have demonstrated it by an intravenous injection of this substance dissolved in water by means of a little soda. Bilirubin kills rabbits in a dose of 5 centigrams per kilogram. We found, moreover, that each of the biliary salts is only one-tenth part as poisonous as bilirubin.

The urine does not carry away the whole of the poisonous matter secreted by the liver; therefore the greater part of this substance must be neutralized in some part of the body. Even if the urine owed the whole of its poisonous nature to bile, the latter would have had to lose five-sixths of its toxic properties in some other way.

This neutralization is effected in the intestines, in the liver, in the tissues, and in the blood.

Schiff thinks that bile does not poison us, because the liver takes it back and rejects it, to take it back and reject it again, and that each time a smaller and smaller portion is absorbed. The true protection seems to me to be the precipitation of the poisonous elements of the bile,—*i.e.*, the coloring matter and the salts,—which, when once precipitated, escape from absorption.

I think, also, that the tissues play a certain protective rôle: they consume and transform the minute portions of bile which, having been absorbed, have penetrated into the general circulation; they fix the bilirubin. The blood consumes the biliary acids.

Is it the same when the bile is reabsorbed into the liver itself? When, in consequence of an osmotic change, the bile passes from the biliary cell into the blood-vessels, the flow of bile extends to the general circulation, and is no longer confined to one region; the protection of the intestines and the liver is suppressed. It is the bile in its entirety that passes from the liver into the blood, and not the part—which is unimportant, from a toxic point of view—which was reabsorbed in the intestines.

The coloring matter and biliary acids will circulate throughout the body. A part will escape through the kidneys, but the greater part goes to impregnate the tissues, the anatomical elements, the normal and pathological humors. The skin, the connective tissue, the hepatic cells, the muscular fibers, the vitreous body, all the epithelial cells, the synovial fluid, and the serous cavities are penetrated with bile. Upon examination, the anatomical elements give two reactions: that of Gmelin for the pigment and of Pettenkofer for the acids. This is what is asserted by clinical and pathological anatomy, but the appearance of these gross manifestations of the passage of bile into the blood is not immediate; emotional jaundice, if it exist, is a rare exception. When we are quite sure of the precise moment of the stoppage of the bile, as in hepatic colic, in which it is indicated by pain, we may easily see that it is often twenty-four hours, or even more, before the icteric tint shows itself in certain mucous secretions and in certain parts of the skin. The urine is colored more quickly. How is it that so long a time elapses before the tint shows itself upon the person himself? This fact seems to contradict the data furnished by experiment.

I make an intravenous injection of bile and kill the animal in a few minutes, without the skin having taken the jaundiced tinge or the urine having been colored. This is an experimental fact that contradicts clinical experience. It has even been asserted that the intravenous injection of bile cannot produce jaundice.[1] Feltz and Ritter never succeeded in obtaining it.

Vulpian injected 250 cubic centimeters of bile into a dog slowly, the injection lasting three days; the animal became icteric. It is true that dogs are often icteric normally. Nevertheless, in Vulpian's experiment the tissues and organs were tinged with bile, and the jaundice was certainly very pronounced.

It is because bile is so poisonous that a sudden injection of bile does not produce jaundice; death ensues before the tissues have had time to become colored. When, instead of bile, a solution of bilirubin only is injected, the five centigrams of bilirubin that are sufficient to kill one kilogram of living animal matter are also sufficient to cause intense jaundice during the few minutes that elapse between the commencement of the injection and death. When the bile is suddenly introduced into the circulation, the coloring matter does not tinge the tissues. A piece of white silk, quickly plunged into icteric urine and washed immediately, is scarcely colored; in this urine still more diluted it is colored in proportion to the duration of its immersion, and the urine is discolored. When the animal is suddenly poisoned, we must consider the quantity of soluble poison that can, at a given moment, produce an impression on the nerve-cells, also the time necessary for the fixation of the pigment on the white tendinous and aponeurotic fibers, etc., in order to color them. In order to color a tissue, time is necessary, rather than concentration of bile.

Once freed from its coloring matter, bile loses part of its toxic property; thus, when bile is injected, if the injection is sufficiently slow, the white fibers, by fixing the bilirubin, protect the nerve-cells. During this time the biliary salts escape by way of the kidneys or are consumed in the blood. We may thus, both experimentally and clinically, obtain icteric coloration without poisoning, providing the injection or reabsorption be slow.

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[1] Vaughan Harley has shown (Brit. Med. Jour., Aug., 1892) that in jaundice, contrary to the hitherto entertained pathological doctrine, the bile which stains the skin and discolors the urine is not absorbed into the general circulation by the blood-capillaries, but solely by the lymphatic system of vessels, and that it does not reach the general circulation by the hepatic veins, but by the thoracic duct. Where the thoracic duct has been ligatured no bile is found in the urine or blood. A similar view is held by Foster, in "Text-book of Physiology," p. 440.—T. O.

Clinically speaking, if all the bile secreted in eight hours were introduced suddenly into the blood, we should see fatal nervous effects produced immediately. But as elimination is incessantly being effected through the kidneys, and as the fibers of the connective tissue are being incessantly colored, while the blood reabsorbs only gradually, nervous accidents are thus averted. The tissues serve to protect the organism against certain poisons. Experience shows us that the most intense form of jaundice, viz.: black jaundice, does not kill, precisely because the coloring matter, which is ten times more poisonous than the biliary salts, becomes fixed.

Thus, in addition to the protection afforded by the liver and intestines, the system finds a protection against biliary poisoning owing to tissues which, as regards functional importance, occupy the lowest rank among the anatomical elements, drawing off from the blood the greater portion of the coloring matter, in order to absorb it themselves. Last, the kidneys also take part in the elimination of the biliary acids; we find, in the urine of those suffering from jaundice, sulphur incompletely oxidized, or in the form of sulphur compounds; this sulphur is derived from the taurin, and should be eliminated by the intestines.

Notwithstanding this elimination through the kidneys, part of the biliary salts, passing through the system, affects the blood-corpuscles, the hepatic cells, the muscular fiber, the epithelial elements, and according as the kidney performs more or less perfectly its work of elimination it causes more or less rapid destruction of these elements. Sometimes only disassimilation is merely hastened, and emaciation is then rapid. Sometimes disassimilation is so rapid that the oxygen that is available ceases to be available for combustion; fatty degeneration then results from the persistence of one of the products of the disintegration of the nitrogenous matter.

Moreover, the retention of the biliary acids acts upon the hepatic cell, which itself undergoes fatty degeneration. Then a new effect is produced, the functional consequence of acute atrophy of the liver, viz.: suppression of the final processes of disassimilation.

The substances disassimilated no longer undergo all the metamorphoses to which they are normally subjected in the liver. The matter that is decomposed no longer takes the form of excrement; the albuminoid substances remain colloid, instead of being crystalloid and therefore dialyzable. Urea, which is an eminently diuretic substance, diminishes; the result is a diminution of renal activity. Now, this is a new danger, a fresh obstacle to elimination. Often also the kidney is affected on its own account by the cause that has produced jaundice,—an infectious malady, for example. But this has to do with quite another kind of poisoning. The liver no longer makes bile, and yet it is not acholia that kills the patient. The poisoning is due to all the causes that are poisoning the system when the kidneys no longer act, and also to those substances that are ordinarily transformed by the liver into excrementitious matter.

The greatest danger in jaundice is renal impermeability. On the other hand, severe cases of jaundice may be cured if the kidneys remain permeable.

# LECTURE XXV.

## MALIGNANT JAUNDICE: AGGRAVATED JAUNDICE.

Importance of the functional and anatomical soundness of the kidneys from the point of view of the cure of jaundice. The various causes that often render the kidneys unhealthy in jaundice.——Consequences of the tissues being impregnated with bile. The diminution and then the suppression of the hepatic functions: the influence of the stoppage of the functions of the liver on assimilation and disassimilation. Accumulation in the blood of the waste products of nutrition incompletely transformed and unfit for excretion. To auto-intoxication by natural poisons succeeds poisoning by anomalous poisons.——The relation of the various accidents attendant upon aggravated jaundice: cholæmia, acholia, uræmia.——The extremely poisonous nature of the urine of patients suffering from jaundice, so long as the kidneys are permeable. Importance of polyuria in the prognosis of jaundice.——Distinction between the aggravated forms of jaundice and the particular malady called malignant jaundice, or acute yellow atrophy of the liver, which is, perhaps, caused by an infective agent, and may be developed without jaundice.

FROM what I said in the preceding lecture on the subject of the causes of the poisoning in jaundice, I showed that there are two poisons in bile,—the biliary salts, which have always been recognized as poisons, and a substance which, up to the present, has not been appreciated, from a toxic point of view, viz.: the coloring matter. This is, I think, a new revelation in pathology. I wish also to call particular attention to the fact that, although in jaundice a considerable quantity of poison enters into the system, nevertheless, in the great majority of cases, this introduction of poison is not followed by death, as the organism is doubly protected.

In the first place, the kidneys carry off part of the pigment and the biliary acids and their derivatives, therefore the urine becomes poisonous; I have found that jaundiced urine kills in the proportion of ten and even as low as seven cubic centimeters per kilogram of the animal. On the other hand, the fibers of the connective tissue retain the most important of the poisons of bile, viz.: the coloring matter. The tissues, by becoming colored, withdraw from the circulation, in increasing proportion, this poison, and exercise gradually a sort of condensing power. Nevertheless, notwithstanding this double protection, we observe, even in mild cases of jaundice, as the first signs of poisoning,—slowing of the pulse, pruritus, nasal hæmorrhages, and rapid emaciation. If the kidneys become less permeable, the conditions of piosoning increase. Now, the kidneys often act insufficiently in jaundice, frequently through a cause that is independent of and anterior to the jaundice itself. Nephritis may supervene and aggravate the malady, resulting often from the same cause that has produced the jaundice,—an infective agent. The liver also may become disordered, like the spleen and the kidneys, owing to infectious agencies having reached it. Last, the impermeability of the kidneys may be the consequence of the jaundice itself altering the epithelial cells. The consequence of the impermeability of the kidney is the retention of the coloring matter and of the biliary salts. The biliary impregnation of the red corpuscles, also of the hepatic cells, muscular fiber, epithelial cells, and the vascular membranes causes destructive modifications in all these elements.

Disassimilation is more rapid or is affected by anomalous processes. The destruction of the cellular elements takes place either totally or by fatty degeneration. We note a diminution in the number of corpuscles; these, too, are swollen and spherical. The serum contains hæmoglobin in solution, not modified. The heart, which is altered in its structure, loses some of its energy; its beats are at first slower, and then feebler and more frequent.

Subsequently atrophy of the liver may set in. Atrophy of the liver is characteristic of one form of jaundice, but does not belong exclusively to it; it may occur even in cases which pass from the benign to the grave form. We note at first a gradual diminution, and finally suppression, of the hepatic function concerned in transforming the materials of disassimilation, as well as those of assimilation.

We must not forget that the liver has a double function. On the one hand, it has to develop the matter absorbed from the intestines—sugar, for instance—in order to form glycogen; if this work cease, the organism is deprived of a substance that is indispensable to it. On the other hand, the liver has to complete the development of the materials produced by disassimilation; before they pass into the excretory channels, colloids should be converted into crystalloid dialyzable material.

Thus, when atrophy of the liver sets in, the repair of the waste of tissue is interfered with, and there is an accumulation of the matter produced by disassimilation, which has not been able to pass into the condition for being excreted. Proteid substances no longer reach the state of urea; therefore the urea diminishes. Now, this is the most important physiological diuretic, forcing the water to pass away through the kidneys and to carry off at the same time other solid excrementitious substances.

While these modifications are taking place in the natural chemistry of the liver parallel chemical modifications of the blood are also going on. An accumulation of leucin, tyrosin, xanthin, and hypoxanthin is produced in the blood and in the tissues. These same substances consequently appear in the urine; and besides other substances, the greater number of which are little known, we find in the urine imperfectly formed albumins, which have not the normal point of coagulation by heat, and which act differently when treated by chemical reagents. The kidney is not constructed for the elimination of these bodies; but, nevertheless, they force their way through the renal barrier.

The biliary function, also, of a liver which is being destroyed by jaundice is soon diminished or suppressed. The liver becomes incapable of forming the pigment and the biliary acids, so that the jaundice itself may diminish and even disappear; the biliary pigment decreases in the urine, and at a given moment, in patients that were at first poisoned by bile, biliary poisoning is suppressed. We no longer find in the urine biliary acids or compounds of sulphur, or the incompletely oxidized sulphur derived from them.

When we administer to a patient suffering from acute atrophy of the liver a substance which, under normal conditions, should undergo certain metamorphoses in the liver,—substances which, like naphthalin, fix the sulphur radicals,—we find that the elaboration of this body—say, naphthalin—is not accomplished according to the normal processes. Instead of being eliminated in the form of naphthyl-sulphite of soda, it is found in cholera patients, for instance—in the urine, in a form which is as yet undefined, notwithstanding M. Rosenstiehl's researches; it gives rise to a particular coloring matter, of a purple-violet tint, similar to that of permanganate of potash. I have observed this coloration, which is due to an anomaly in the elaboration of the naphthalin, in acute atrophy of the liver and in two cases of typhoid fever. Thus, when the liver is destroyed, disassimilated substances are defectively elaborated; the chemistry of malignant jaundice confirms this, and this particular case of the anomalous elaboration of naphthalin in acute atrophy of the liver and cholera furnishes a still better demonstration.

Besides the disorders resulting from the suppression of the hepatic functions in malignant jaundice the kidneys, if not already disordered, soon become so. In the same way that lead, silver, mercury, and cantharides, when being eliminated, cause true toxic nephritis, so do the biliary poison and the poisons fabricated in a secondary manner, by imperfect disassimilation, during their elimination, produce renal changes. This is, then, a fresh hindrance to renal ejection, and a new cause of the retention of poisons in the system. Last, the vessels also become affected; extravasations are produced, and in some cases, which cannot be called exceptional, renal hæmorrhage still further increases the impermeability of the kidneys. Thus, while the chances of biliary poisoning diminish, causes of secondary poisoning appear, which continually increase in consequence of the renal impermeability, the anomalous elaboration of the liver, and the alteration of all the cells of the body.

Auto-intoxication by natural poisons is succeeded by self-poisoning by other morbid poisons. If objections are raised to this singular complexity of the phenomena, if I am blamed for substituting for the too simple and natural idea of the pathogenesis of the serious accidents attendant upon jaundice, owing to the action of the biliary salts, that of the train of processes which take place one after the other in natural sequence, I shall answer that not a single link in this chain can be shown to be false, and that the truth of each separate detail can be established. Only the degree of their subordination is left in doubt.

Now, with regard to jaundice that has become serious, we are obliged to appeal to this succession of the various processes. I cannot affirm positively that such and such a succession is the absolute order of facts, but I firmly believe that they all play an important part, and I am inclined to believe that the order of complications is as follows: Biliary poisoning (cholæmia); cell-degeneration, particularly alteration of the hepatic cells; atrophy of the liver and suppression of its functions (acholia),—renal changes from various causes, ending in renal inadequacy; last, self-poisoning, of a mixed nature, through acholia,—*i.e.*, through the retention of anomalous toxic products; and through uræmia, —*i.e.*, through the nonelimination of the normal toxic products, which should be carried off by the urine.

This uræmic element cannot always be compared with ordinary uræmia; it cannot be uræmia from an alimentary cause, the patients being scarcely nourished at all; nor can it be poisoning from reabsorption of bile, since the latter ceases to be secreted; the putrefactions of intestinal origin certainly contribute to it as one cause, but it is principally a poisoning by the normal or abnormal refuse thrown off by intense disassimilation, setting free potass,—which is quite capable of poisoning and of causing convulsions in a large number of cases,—and also organic matter incompletely elaborated. Thus, the greatest danger in severe jaundice is the impermeability of the kidneys. If the kidneys remain permeable, the patients discharge urine that is intensely poisonous, and which has a great tendency to cause convulsions. This urine, even when decolored by carbon, retains its convulsive power; it is sufficiently powerful to kill animals in opisthotonos, as if they were poisoned by the potass that has been sent in excess into the blood through the exaggerated disassimilation of the tissues. If the kidneys are no longer permeable, the urine will no longer have this convulsive power, but the patient will be poisoned and have the convulsions.

As long as renal impermeability is not manifested, the prognosis may be reserved in severe attacks of jaundice, and complete recovery is possible. In certain cases, after having observed the hepatic dullness diminish every day, we then see it return by degrees to its original limits, showing that the liver has regained its volume in the space of a few weeks or a few days. I have personally remarked two instances of this kind. The severe jaundice was not then complicated by renal lesions; the polyuria remained constant, and from three to four liters of urine were secreted daily. Is all that I have said applicable to the particular malady which Rokitansky has called acute yellow atrophy of the liver? to the form of severe jaundice described by Ozańam? to the typhoid jaundice of Lebert? to the essential hæmorrhagic jaundice of Monneret? or to the essentially grave jaundice of Genouville? I do not think so. What I have said applies to simple attacks of jaundice that have become severe; moreover, these are perhaps the most common class.

According to Frerichs, the primordial cause is atrophy of the liver, which, by vitiating the elaboration of the various kinds of matter, produces all the other complications. Other hypotheses have been proposed. We need not discuss jaundice proceeding from the suppression of the hepatic function, no more than jaundice from polycholia or from too great activity of the hepatic function, the jaundice in these cases being only slight, of short duration, or absent. At least there have been as many theories formed about severe jaundice as about uræmia.

Buhl's theory is that severe jaundice is the result of cerebral œdema; that, elimination of water by the bile being suppressed, hydræmia ensues, and then cerebral œdema. Can we admit that the 800 or 1200 grams of water in the quantity of bile formed daily can produce such effects when we know that, normally, the intestines reabsorb half or two-thirds of this water?

Uræmia alone is to be considered the cause, according to another opinion. I have taken it into account, as you know, but we can only trace its terminal complications. There only, then, remains acholia,—the suppression of the part played by the liver in disassimilation; this is Frerich's theory, and I believe it to be the correct one.

But what can produce the atrophy of the liver? Everything tends to show that it is the consequence of a general infective malady, not only because infectious agents have been found in the fluids and the tissues, but because at the same time we find fever; purpura; a polymorphous erythema; scarlatiniform, circinate, and globular eruptions on the skin, the pharynx, and the palate; and because an acute nephritis exists, with parallel determinations to the various viscera.

Jaundice does not necessarily supervene in acute yellow atrophy of the liver, but it may form a connecting link between the destruction of the hepatic cells and the appearance of a nephritis, which adds to the symptomatic list its own contingent of accidents traceable to uræmia. The study of severe jaundice thus serves as an introduction to the study of poisoning by anomalous products.

# LECTURE XXVI.

## THE TOXIC NATURE OF PATHOLOGICAL URINES.

**Causes of death in infectious diseases. Examination of the poisons in the tissues of animals that have died from infection. The toxic nature of the urine in tetanus. Special characteristics of the toxicity of the urine in fevers; convulsive properties. The part played by poisoning in the ataxo-adynamic accidents of fevers and in the death-struggle.**

WE know that in the course of infectious diseases there exists a perversion of the nutritive processes, more particularly in the function of the liver-cells. Under the influence of the disease we note the appearance in the urine of anomalous material, the products of imperfect disassimilation, colloid substances, and modified albumins. We find drugs undergo unusual transformations, naphthalin, for instance, being eliminated without having entered into combination with sulphur. Some of these anomalous products may be poisonous; but this is only a matter of conjecture, requiring demonstration. This task is not an easy one, and often ends in a negative or doubtful result.

I have long endeavored to find the substance which causes death in infectious diseases. If, in certain cases, death may be attributed to the withdrawal of oxygen from the blood, as in charbon; to capillary obstructions in the more important organs; to septic foci being established by the infectious agents passing out of the vessels, the explanation, in the majority of cases, lies in poisoning. I have found hardly any trace of those poisonous substances that are well known, especially in infections of digestive origin,—surface infections. I found that the alkaloids were increased, but that they could only account for a very small part of the auto-intoxication. I have searched for this poison in gaseous gangrene. Charrin has also endeavored to find it while studying the form of septicæmia that will in future bear his name.

Extracts were taken from all the organs of five animals that had died of septicæmia. These extracts were injected into healthy animals and produced poisoning, but with extracts from the organs of healthy animals we also obtain poisoning. Does not the destruction of the anatomical elements allow substances to become free that are held in the living cells by the forces of tension? The normal poisons have thus prevented the discovery of the anomalous poison. Of the substances that may be suspected we have particularly studied the alkaloids. We have extracted alkaloids from the bodies of animals that have died of infectious diseases; we also find alkaloids in the tissues of healthy animals, although, perhaps, in smaller quantities. However, the quantity of alkaloids extracted from the bodies of five animals that had died of septicæmia was not sufficient to produce poisoning. We have not, therefore, succeeded in finding the morbid poison that kills in infectious diseases, but these negative results do not alter the fact that we must admit the existence of such a poison in these cases. How, for instance, can we explain the fact that gaseous gangrene, which is so eminently infectious, but which only produces local anatomical injury, without embolism or any inflammatory process, can cause death, if it is not that, simultaneously with the production of œdema, a poison is fabricated which kills the higher elements of the system? This is mere hypothesis, it will be said. Yes, but hypothesis that is almost necessary.

Not having been able to select one single poisonous substance that could really be considered capable of producing the effects referred to, I endeavored to study the poisonous element as a whole, taking all the poisonous substances in the eliminating liquid,—the urine. By proceeding in this manner, I arrived at results that seemed to me to be convincing.

A patient attacked with tetanus passed no urine for two days. M. Labbe collected the urine when it reappeared. On being injected into the veins of an animal, it produced mild tremors after the sixth cubic centimeter; myosis appeared; the pupils were punctiform at ten cubic centimeters. After twelve cubic centimeters there were violent tonic spasms and convulsions up to the thirty-fourth cubic centimeter; death then ensued from opisthotonos. Is not this almost a complete reproduction of the symptoms of tetanus? We then thought that the urine contained a convulsive poison, which was the cause of the tetanic convulsions. We were half inclined to see in this the confirmation of the infectious nature of tetanus. This theory was very tempting. But when we studied the toxic properties of the urine in pneumonia in six cases, we found at once that it is more poisonous than normal urine; it is capable of killing in the proportion of nineteen cubic centimeters per kilogram of the animal, as a minimum, the average proportion being thirty-eight cubic centimeters. We observe in the animal the ordinary signs of poisoning by normal urine,—myosis and lowering of temperature; but, besides these symptoms, we get tonic convulsions absolutely similar to those produced by the urine of a patient suffering from tetanus, spasms with lasting muscular rigidity, and, finally, death from opisthotonos. The urine of patients suffering from pulmonary splenization killed animals, when injected in quantities of twenty-two cubic centimeters, with the same convulsions. In typhoid fever, at its commencement, before intestinal antiseptic action has yet been effected, I have seen the urine produce only those toxic phenomena that belong to normal urine,—no convulsions, very little pupillary contraction, narcosis; death ensues at fifty, sixty, and seventy cubic centimeters.

In lead poisoning sixty-six cubic centimeters of urine per kilogram have produced death without convulsions. In leucocythæmia the urine has caused death in convulsions at fifteen cubic centimeters. The urines of those suffering from jaundice cause death with convulsions; the fatal result might in this case be attributed to the substances of biliary origin, the acids, or the coloring matter; but I have reason to think that death is due to another cause. The urine of albuminuric patients not suffering from uræmia causes death at fifty-four cubic centimeters without convulsions. The urine of those attacked with uræmia is no longer poisonous.

From all these experiments it follows that in certain chronic diseases the toxic nature of the urine is the same as when it is in a normal condition, and that the symptoms are the same as those produced by normal urine; but in the greater number of pathological urines, and in that of all feverish diseases, we find an increase in the normal degree of toxicity, and also new toxic properties, especially the power of producing convulsions. The urine of fever patients has all the characteristics of normal urine, with less somnolence and with the addition of convulsions. The convulsive tendency is no doubt present in normal urine, but as long as the convulsive poison and the narcotic poison are in conjunction the latter annihilates the former. It is possible that normal urine might be capable of producing convulsions if the narcotic poison were withdrawn. Thus, the injection of the urine of those suffering from disease produced neither the repetition of the symptoms of the disease nor the reproduction of the disease itself. Nevertheless, I once found that the urine of a patient suffering from phthisis produced tuberculosis. Landouzy quotes a similar case, and Toussaint also. Before that occurred, he had observed the reproduction of charbon by inoculation with the urine, and Charrin succeeded in reproducing his septicæmia by the same means. We reproduce, by the injection of urine, those infectious diseases that can be transmitted to animals, and in which the infectious agents are eliminated through the kidneys. What I thought to obtain by the injection of these pathological urines was not the transmission of the disease, but the reproduction of some predominating symptom. I did obtain an anomalous symptom, but this was produced indiscriminately by the urine of tetanus and that of pneumonia. In the case of diseases that are not infectious, or those in which the microbes are not eliminated through the kidneys, how can we explain the greater toxicity of the urine and that special convulsive property which we find is common to nearly all febrile or consumptive diseases?

Has the disease, by perverting nutrition, generated poisonous substances? In pneumonia, is some alkaloid or other poison formed? This question is at present unsolvable. Moreover, if we admit that special toxic substances are formed by the disease, how can we explain the fact that all diseases shall produce the same convulsive poison? Another hypothesis is that the pathological urines owe their toxic nature to certain normal poisons produced in superabundant quantities. Several substances produced by normal disassimilation may cause convulsions. If alimentation is suppressed in feverish diseases, disassimilation is

The weight of the body sometimes diminishes several in twenty-four hours. Now, the destruction of the s free potass, a substance that causes convulsions. In ever the urine, which is only slightly toxic at first, when is being slowly destroyed and the weight of the patient ely diminished, becomes decidedly poisonous at the period avalescence, when rapid emaciation takes place. This is argument in favor of the hypothesis in question.

The coloring matter is increased in the urine of fever pa-nts; for instance, from six to sixty and eighty in twenty-four hours. Now, highly colored urine causes contraction of the pupil and convulsions; on being decolored by charcoal they lose their convulsive property. However, the convulsive power of certain pathological urines does not disappear from them under discoloration, which proves that, in these cases, the convulsions are due, to a large extent, at least to potass, and not exclusively to convulsive organic matter. Is it not a striking fact that febrile urine, in which the coloring matter is from ten to twenty times as abundant as in normal urine, becomes so intensely convulsive? We also note in fever a diminution in the salts of alimentary origin,—chloride of sodium, for instance. Potass, on the other hand, is doubled or trebled. In short, then, what fever does is to pour in excess, into the blood and the urine, potass and coloring matter, or at least toxic substances which are habitually associated with coloring matter. Now, potass and coloring matter are powerfully convulsive; I am, therefore, inclined to think that the urine, in acute diseases, owes its toxicity not to a special poison, but to certain normal poisons in excessive quantities. Febrile urine produces the same phenomena as normal urine, only more quickly, myosis, polyuria, lowering of temperature. Somnolence appears very tardily; the effect of the narcotic substance is diminished, it being overpowered by the convulsive poison. The latter, when produced in excess, quickly manifests its power, which, under normal conditions, is concealed by the narcotic poison.

How is it that these substances, which render the urine poisonous, do not poison the patient? Precisely because the urine is poisoning,—*i.e.*, because it carries off the poison. But if the kidneys begin to work defectively, complications appear—convulsions, the final ataxo-adynamic phenomena of every disease—which may result not only in secondary nephritis, but also in an insufficiency of urine during the death agony. The death struggle is a form of poisoning, as all the signs observed in the dying testify, from the pupillary contraction which appears at first to the final convulsion and the last throe.

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The coloring matter is increased in the urine of fever patients; for instance, from six to sixty and eighty in twenty-four hours. Now, highly colored urine causes contraction of the pupil and convulsions; on being decolored by charcoal they lose their convulsive property. However, the convulsive power of certain pathological urines does not disappear from them under discoloration, which proves that, in these cases, the convulsions are due, to a large extent, at least to potass, and not exclusively to convulsive organic matter. Is it not a striking fact that febrile urine, in which the coloring matter is from ten to twenty times as abundant as in normal urine, becomes so intensely convulsive? We also note in fever a diminution in the salts of alimentary origin,—chloride of sodium, for instance. Potass, on the other hand, is doubled or trebled. In short, then, what fever does is to pour in excess, into the blood and the urine, potass and coloring matter, or at least toxic substances which are habitually associated with coloring matter. Now, potass and coloring matter are powerfully convulsive; I am, therefore, inclined to think that the urine, in acute diseases, owes its toxicity not to a special poison, but to certain normal poisons in excessive quantities. Febrile urine produces the same phenomena as normal urine, only more quickly, myosis, polyuria, lowering of temperature. Somnolence appears very tardily; the effect of the narcotic substance is diminished, it being overpowered by the convulsive poison. The latter, when produced in excess, quickly manifests its power, which, under normal conditions, is concealed by the narcotic poison.

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If this subject could be studied like the pathogenic agent of blue pus, it could perhaps be more easily explained. Blue pus is characterized by two things,—a body having the chemical characteristics of the alkaloids, and which has long been recognized, viz., pyocyanine; and a microbe, a mobile bacillus, which produces this substance, and which is mentioned by Gessard. The microbe is easily recognized, since the blue color of the substance that it fabricates betrays it wherever it is met with. The blue is completely fixed by chloroform; afterward, in the presence of acidulated water, the chloroform is discolored and the water takes a roseate tinge. By this reaction we can always recognize this organism, which develops rapidly and resists the action of all the other ferments.

Taking advantage of this characteristic, M. Charrin has made experiments in inoculation and injection with liquid cultures. Clinical surgery has shown that blue pus, when brought into contact with a wound, does not produce infectious accidents; but, it may be asked, what would happen if it forced its way through the barrier of the tissues? This hypothesis has been answered by the injection into the veins of pure "culture liquids" containing both the microbe and pyocyanine. The subcutaneous injection seems harmless, but an animal that is subjected to an intravenous injection of 1 or 2 cubic centimeters of liquid, prepared in this way, becomes feverish and ceases to eat; it may be attacked with intense albuminuria and diarrhœa; it becomes emaciated and ill. We must mention that a certain number of rabbits prove refractory, and that often considerable doses are required in order to succeed. Is this malady of an infectious nature? We know that microbes are eliminated by the urine and fæcal matter. But are they still alive? Yes; since we observe, simultaneously with their presence, the reaction of pyocyanine in the liquids impregnated with these substances.

We may push the question still further, and, by treating the bacillus and the chemical substance separately, we may endeavor to ascertain their respective rôles in the mechanism of the disease. We withdraw the microbes from the liquids in which they have been cultivated, employing for this purpose either heat and filtration or filtration by means of tested Chamberland cylinders[1]; we find in the filtered liquids all the reactions of pyocyanine, and we can, moreover, make sure by cultivation that these liquids no longer contain any microbes. If, under these conditions, we inject into the veins of a rabbit the filtered liquid, which is rich in pyocyanine, we find that the toxicity of this liquid is comparatively slight, whether we inject successive quantities for several days, or whether we inject at once 60 cubic centimeters of the liquid. The animals, upon receiving these injections, which are made antiseptically, show only transitory effects, and in some cases can be cured; whereas, when the same liquids, containing microbes, are injected in the same animals, these animals, as I have said, become diseased and generally die. We are thus led to think that in the development of this experimental disease, while taking into account the action of the chemical substance, we must also consider the material lesions, nephritis, enteritis, etc., which seem to be created by the microbe itself. To speak of nephritis only, for instance, we do not always produce it in a lasting form, by injecting into a rabbit, in a certain quantity, crystallized pyocyanine, or a liquid containing pyocyanine deprived of microbes; whereas, when we inject a liquid culture containing microbes, if the animal survive a certain number of days, nephritis is established permanently, and microbes are found in the blood, the kidneys, and the urine. Under these conditions the blood, the kidneys, or the urine, on being treated, show the presence of pyocyanine. It is, therefore, from these experiments, probable that the microbe, besides its possible chemical action, produces a traumatic effect on the kidneys and causes a nephritis, which then acts on its own account, and places the animal in the position of a patient attacked with Bright's disease.[2]

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[1] See Wilson's "Hygiene," page 232.

[2] The results indicated were obtained by experiments on the rabbit; we are not speaking of those that can be obtained upon other animals,—the guinea-pig, for instance,—and by varying the modes of introduction. The results in these cases may be different, and this is not surprising, since the conditions of the experiment are changed. M. Charrin is of opinion that fresh reservations should be made as regards the rôle of the chemical substance. Recent experiments have shown him that the

We must now endeavor to find out whether the poisons are produced in consequence of a disordered state of the general nutrition.

As regards sugar, the formation of which is considered by certain physicians as the result of a disordered state of nutrition of the liver, can we look upon it as a poison? Not in my opinion. Sugar is not essentially poisonous; it only becomes injurious by its quantity. If it is not consumed, transformed, or destroyed by the organs, it becomes a poison like carbonate of soda, which, in excess, may become poisonous although it forms an integral part of the blood. As long as the blood contains only 1 in 1000 of sugar, the system is not appreciably affected; but above 3 per 1000 (Bernard) or 5 per 1000 (Pavy) the effects of poisoning ensue, and a special pathological condition is established.

One of the first symptoms of excess of sugar in the blood is glycosuria, which does not exist when there is only 1 per 1000 of sugar in the blood. When this proportion is increased, the hyperglycæmia deranges the quantity of the urine. In fact, when sugar is eliminated, it carries away its equivalent of water of diffusion, which is in the proportion of 7 parts of water to 1 of sugar. Under normal conditions, the blood does not allow itself to be dehydrated; when it gives up a portion of its water, it recovers it immediately by drawing it from the plasmas and the elements of the tissues. The blood cannot have less than its normal percentage of water; in order to supply the renal secretion, it must be incessantly receiving water, which is either conveyed to it by drinking, or which it draws from the tissues and especially from the plasmas, which represent in weight a third of the economy. If the water obtained by drinking and the water from the plasmas fail to keep up the required supply, under any other circumstances than the case of hyperglycæmia the renal secretion could be diminished or suppressed. But as long as there is in the blood water and sugar in excess, there is produced

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pyocyanine bacillus could live under certain conditions without generating pyocyanine itself. It is, therefore, possible that in the animal a body is formed which is more or less like pyocyanine, but possesses a different degree of toxicity and acts differently.

a glycosuria accompanied by the water of diffusion due to the sugar; when the glycæmia is intense, the sugar, which must necessarily be supplied with its equivalent of water of diffusion, dehydrates more and more the plasmas and the tissues. One of the primary effects of poisoning by sugar is, therefore, the extraction of water from the system. Then a modification is produced in the phenomena of osmosis; the sugar, having rendered the blood more dense, becomes a fresh medium for the elements of the system, and is thus another cause of the abstraction of water from the plasmas. We find the sensation of thirst appear. A diminution ensues in the aptitude of the water to leave the blood; the pulmonary exhalation diminishes as well as the cutaneous exhalation.

Under normal conditions one-third of the total quantity of water that passes out of the system is eliminated by the lungs and the skin. In a diabetic subject, according to Bürger, these emunctories only eliminate one-twelfth.

Among the consequences of this dehydration of the tissues we must note diabetic cataract, which has been demonstrated by an ingenious experiment performed by M. Lecorché. This is the explanation that is generally admitted; but in reality the crystalline opacity which is produced experimentally by dehydrating the body by means of sugar or salt is not cataract; it disappears when the tissues have regained their normal percentage of water. Diabetic cataract, on the contrary, is permanent, and we not infrequently see it developed in patients that are suffering from œdema, in which case there is no question of dehydration.

As results of the derangement of nutritive processes, we note the appearance of anomalous products of disassimilation, anomalous albumins, so frequent in diabetic subjects, and an increase of the extractives or urea; these features are not the unfailing rule, but they are accidents that might be explained by hyperglycæmia.

The dehydration of the tissues, when it exists only in a moderate degree, provokes certain functional disturbances, which, in the nerve elements, take the form of an exaggerated excitability and rapid fatigue, and which in the muscular elements are manifested by cramp, as in cholera. A higher degree of dehydration is attended by nervous accidents of great gravity, in which category we may perhaps include diabetic coma.

When we were discussing typhoid fever and dyspepsias, we mentioned a particular alteration of the fluids, in consequence of which the breath exhales an odor similar to that of chloroform or rennet-apples, and also a particular chemical reaction of the urine. It has been suggested that this odor of the breath and this reaction of the urine may belong to acetone.

In certain urines a few drops of perchloride of iron will give a claret-colored tint, or the shade produced may be darker, even violet. The reddish-brown tinge is very frequent under various morbid conditions; this is due to substances the nature of which has not been chemically defined; acetone gives a wine-red color, but this tint may be produced by other substances. This reaction is met with in certain forms of dyspepsia, in typhoid fever, scarlatina, leucocythæmia, and in pernicious anæmia; it is very frequent in diabetes. Nevertheless, in many diabetic subjects, we may observe for years the chloroformic odor of the breath, without ever detecting it in the urine, and still rarer in this disease is the reaction of perchloride of iron. If a salt due to the combination of diacetic ethyl with soda resulted from the transformation of the acetone, we should obtain the coloration without the odor; otherwise we get the chloroformic odor in the urine without the coloration. In short, in nearly all cases of diabetic coma, perhaps in all, we find the color-reaction of the urine and the odor of the breath. It is therefore probable that in these cases poisoning exists similar to that of severe dyspepsia. I know nothing of the pathogenic conditions of those forms of poisoning termed acetonæmic. The clinical fact having been observed by Brieger, at the clinic of Frerichs, under various pathological conditions; by Senator, by Jaksch in carcinoma of the stomach and in severe forms of dyspepsia, and by myself in typhoid fever and in a very great number of cases of dilatation of the stomach, it seems to me probable that the cause of it is some morbid substance elaborated in the intestines. These accidents can be reproduced in every feature experimentally, as has been shown by the experiments of M. de Gennes.

However this may be, we note in certain diseases, not necessarily infectious, a body, or a series of bodies, which, on being eliminated by the urine, give a red coloration upon the addition of perchloride of iron. These bodies are the result of the defective elaboration of matter by the human organism; they are anomalous substances, not engendered by microbes. Among these substances are acetone, diacetic ether, and oxybutyric acid, which are poisonous; thus we find in this class some true morbid poisons. In diabetes this reaction of the urine and the odor of the breath may serve as a basis of diagnostic and prognostic indication.

Two years ago the odor of the breath enabled me to form the diagnosis in a case in which a child had been suddenly attacked with comatose symptoms. It was not known that the child was ill when he was brought home from school in a state of complete coma. The skin was dry, and there was no patellar-tendon reflex. Guided by the odor of the breath and the absence of the reflex, I expected to find sugar in the urine; but, as the child passed no urine, I had those parts of his clothing washed that were likely to be stained with urine; in the infusion thus procured I obtained the reaction of sugar, and was thus enabled to pronounce the attack to be diabetic coma, which ended in death in a few hours.

# LECTURE XXVIII.

## POISONING BY PATHOLOGICAL POISONS. CHOLERA.

**Former opinions as to the causes and the nature of cholera. Influence of the prevailing pathogenic theories on the choice of prophylactic modes of treatment. Mode of propagation of cholera. Importance of the transmission by water. Other possible modes of contagion. Attempts to discover the agent of infection. The French Commission in Egypt. The researches and opinions of Koch. The value of the comma bacillus. Studies of the transmissibility of cholera to animals.**

IN studying diseases caused by poisoning I am naturally led to speak of cholera and to sum up the knowledge that we possess of its nature. All that has been said with regard to the etiology of the plagues of antiquity and of the Middle Ages has been repeated in modern times with regard to cholera. It was at first attributed to the wickedness of man and the anger of God; to this religious view succeeded the idea of poisoning by means of witchcraft, a theory to which were attached corollaries of certain practices that were reputed to be prophylactic. Wells and springs were believed to be poisoned. Certain persons, and especially doctors, were accused of being the promotors of direct poisoning. These absurd accusations were made in Paris in 1832 and in Naples in 1884. In the past, Jews and doctors were often associated together in public denunciations relating to pestilential diseases. They were suspected of poisoning food. Travelers generally were also suspected,—not only those who were infected, but all foreigners; a foreigner was looked upon as a deadly enemy. Previous to the pestilence being attributed to water, the air and the clouds had been made responsible for it; there was a time when a certain cloud hovering over a town was reputed to be pestilential in virtue of some peculiar reflection or some unusual tint. These ideas were prevalent in the fourteenth and fifteenth centuries, and we have actually seen them revived in the second half of the nineteenth century! Naturally the prophylactic measures proposed were in harmony with these etiological chimeras. It was necessary to avert the divine wrath by expiatory deeds, by penances and fastings imposed on evildoers. Believers in the efficacy of pilgrimages and processions are to be found, even at the present day, in all classes of society.

People were more practical during the Black Plague; they appointed sentinels to guard the wells. In Paris also, in 1865 and in 1873, I noticed that the casks of the water-carriers on the Quai St. Bernard were guarded by the police. Was this a concession to popular prejudices on the part of the authorities, or did the authorities share these prejudices? Sentinels were also placed at the gates of towns, the portcullis was lowered and the drawbridge raised. In our own times sanitary cordons have been drawn up round uninfected towns in the south and travelers have been received with gunshot.

Yet a calm examination of facts has shown that cholera is a disease that is endemic in certain countries; for centuries it has been prevalent on the Delta of the Ganges. Thence it spreads; it follows a caravan and marks the route from the Ganges to Mecca, where it attacks the Mussulmans, Hindoos, etc., assembled together; on its return it rages among all the caravans, sometimes completely destroying them, or it advances with them as far as Hedjaz and Persia; it then continues its migration through Russia to Western Europe. Its progress has also been traced from Hedjaz into Egypt, to Alexandria, where it forms a fresh center, thus menacing Europe from two sides. We know that its migrations are determined by commerce and by routes followed by the great human currents,—seas, rivers, roads, and railways.

What strikes us in the history of cholera, when we hear of its having appeared almost simultaneously at several points, is that it is always a sea-coast town that is first attacked. It never appears first in an inland district.

With regard to this, it has been asserted that, in a certain number of instances, a port has been infected without any patient suffering from cholera having disembarked there. But even if the infection is not conveyed by those who have been attacked, the ship itself has been contaminated or brings infected linen. The corpses of those that have succumbed to the disease may have been thrown into the sea, but the discharges and the linen impregnated with them have remained on board. In these cases the linen has never been disinfected; the truth has not been told as regards this matter. We can see how much importance may be attached to the official statements relating to the disinfection of suspected ships or cargoes by the pretense of disinfection that we witnessed during the last epidemic. The authorities did right not to insist upon the disinfection of the people themselves; I am not so sure that they were justified in not ordering the thorough disinfection of clothes, linen, and bedding after landing; it was then too late. But at the lazaretto how did they act? They did not even demand that the people entering the lazaretto should take a bath.

Since that time a great outcry has been raised against us by the public and the press, and public authorities have been shaken in the confidence they had placed in doctors, and have begun to ask themselves whether the latter had ever deserved this confidence.

Often still, when we follow the dissemination of cholera through France, we can trace it to linen that has not been disinfected. On studying the history of a great number of local epidemics, we find that laundresses have been attacked first. The dissemination of cholera has also been attributed to water. It is probable that several centers have been created by this agency. It is almost an established fact that, in towns, the districts that have escaped have been those which could not come into contact with the discharges of those attacked, conveyed through the medium of water; on the other hand, our canal of the Ourcq, with its array of boats, was one of the most powerful agents of transmission—at any rate, in the last epidemic; and the districts first attacked were a part of the Faubourg Saint-Antoine and the Rue Sainte-Marguerite,—those to which the water of the Ourcq was brought by direct canalization.

In hospitals where water is economized, where infected and unfiltered water might be used for culinary and pharmaceutical purposes,—at La Charité and at Lariboisière,—cases occurred within the building before any cholera patient from the town had been brought to the hospital. To the same cause may be attributed the disastrous infection of the Asylum for Old People, in the Rue de Breteuil. As regards the other centers of infection, it is impossible to explain their origin categorically, on account of the mixing of the water of the Dhuys and the Vanne with that of the Ourcq, in consequence of the ansastomoses which are the great fault of our system of canalization, and which cause an ebb and flow from one stream to the other.

With regard to the spreading of infection by water we cannot believe that there is any truth in the assertion that the infection may be conveyed up the river, along the Rhone for instance, from Marseilles to Avignon; no one, on reflection, can admit that the germs could be carried against the stream.

The link that is missing in the chain of evidence of contagion is direct contagion. But if measles, small pox, and scarlatina are spread chiefly in this way, we can understand that with typhoid fever and cholera the infection is conveyed not through the body itself, but through what comes from the body. We must also take into account the vegetables that grow close to the earth and that are eaten raw, and various modes of contamination by drinking. We have naturally been led to consider cholera as a disease that is indirectly contagious, like typhoid fever; it was natural, therefore, to look for the agent of contagion in cholera. The pathogenic study must be entered upon from a parasitic point of view, and, in fact, the first reports of the discovery of organisms said to be infectious date from 1848. These first reports have no scientific value, but they serve to show the spirit in which the investigations have been carried on since that time.

Virchow in 1848 and Hallier in 1867 found frequently parasitic organisms in liquids where microbes constantly exist. Regular, systematic investigations did not commence until the European commissions were sent to Alexandria in 1883; these researches were instituted by the French Commission, which included in its members Messrs. Straus, Roux, Nocard, and Thuillier, and by the German Commission of R. Koch. The great secrecy observed by the French Commission was fully justified. At first, it is true, the telegraph told too much; but when the members of the Commission spoke themselves, they expressed their doubts at the right time. They had found traces of an organism in the blood, but they added that this differed singularly from the various ferments known, not being colored by t ordinary processes and not being susceptible of cultivation.

Koch has also, on the other hand, discovered an organism the form of a comma, which cannot be classed under any of t five groups of ordinary parasitic intestinal microbes. Th comma-shaped organisms appeared to him to be on the surfa or in the interior of the intestine of cholera patients, and th are sometimes in such quantities as to constitute nearly t whole of the excretions. Koch has seen them in the cholera discharges, on the cells while desquamation is going on, or b tween them and penetrating into the interior of the intestin glands and into the superficial parts of the mucous membran but he has never found them anywhere else, having searched f them vainly in the ganglia, the kidneys, the spleen, the bloo and the lymph, and yet he has already asserted that these orga isms are the pathogenic agents. The comma bacillus is a sho slender, moving body, which fixes certain stains like other path genic organisms. The examination of this germ presents n difficulty. It is slightly curved; its dimensions are as follow length, from $1\,{}^{1}/_{2}$ to $2\,{}^{1}/_{2}$ microns; breadth, from 0.6 to 0 microns. These comma microbes may be found linked togeth by twos or threes, so as to form a little chain; they may b curved in opposite directions or in the same direction, so as appear in the form of an S, or of part of a circle, or they ma assume a spirillar form. Such is the statement of Koch, whi rests solely on the empirical fact of his having found, on th surface of the intestine, an organism which is not present unde ordinary conditions, and which is very abundant in choler But it has yet to be explained how this organism causes the di ease. Koch says that, after it has left the intestine, he can con tinue its germination on any moist surface, on the surface o food, and on the soil when the temperature is not too low an when the atmosphere is damp. The question then arises as t how a district is ever freed from it. The fact that a lake con tained any of these organisms would be sufficient to render permanently infected, and Koch actually discovered in Indi a lake the waters of which contained these comma bacilli, whic he was able to cultivate; in this way there would be a perpetu interchange of infectious germs between the earth and man. This explanation is simple; in fact, it is too simple to be admitted. If it were true, how is it that in Paris and in Germany, where the cultivation of cholera germs has been studied unceasingly, the various laboratories have not been infected? How is it that the disease has not broken out among the experimentalists?

In order to distinguish the bacillus which he has found in those attacked with cholera, Koch has endeavored to find certain special characteristics—a different action on gelatin, and a particular configuration in the zone of liquefaction—which would reveal the nature of the bacillus. This characteristic, however, is not wholly convincing.

It must be remarked that the same organism has been found in cases of sporadic cholera by Finckler of Bonn; it was, perhaps, somewhat larger than Koch's bacillus. Thus, in two diseases which resemble each other in their symptoms to such a degree that the most learned physicians do not express a decided opinion as to the nature of the accidents attendant upon them until after the extension and propagation of the disease, we find microbes exactly similar in form. Against the pathogenic value to be attached to the comma microbes it has been urged that as they exist only in the intestine, they could not so rapidly cause such serious general disorders. But it may be that these organisms engender a toxic substance which, when once absorbed affects all the cells of the system.

Other investigators—M. Emmerich at Vienna and M. Doyen here—think, moreover, that they have found pathogenic microbes in some of the viscera. M. Emmerich, who states that he has seen them, did not recognize among them the comma bacillus. M. Doyen, not having absolutely detected them in sections, draws conclusions from sterilized cultures made with portions of the liver and kidneys, in which the existence of the microbe was not shown by the microscope; these cultures had reproduced the comma bacillus.

All this consists merely of hypothesis. I am ready to grant that the comma bacillus may be a microbe that is peculiar to cholera, although it has been found in the saliva of people not suffering from that disease. But what conclusions can be drawn from the discovery of this microbe? It has been cultivated, but these cultivations have not succeeded in reproducing the disease. Is it likely that the result, which could not be obtained even from the discharges of the patients themselves, could be obtained from the supposed agent of the infection of cholera, cultivated and isolated, when not an atom of the organism of the person attacked with the disease had been removed with it? Since 1865 and 1866 attempts have been made to produce cholera experimentally with the perspiration, the vomit, and the discharges of cholera patients. The experimentalists have succeeded in killing animals, probably by communicating to them certain forms of septicæmia, but not by reproducing cholera; and yet they hope to succeed by the introduction of the great-grand-nephews of microbes that have been taken from material that will not of itself produce cholera!

It was thought that the failure of the experiment was due to a defective method of introducing the pathogenic organisms into the intestine, because they did not avert the protecting influence of the gastric juice, the acidity of which would prevent the development of the microbes. Now, since 1832, it has been erroneously asserted that the choleraic discharge is always neutral or alkaline; I have found it to be acid. The acidity of the intestinal liquid was slight, but was still present at the moment of death. This fact contradicts the theory of the supposed protective influence that would be exercised by the gastric juice. Moreover, if animals do not take cholera when choleraic matter is introduced into their stomachs, how is it that the disease is conveyed through the gastric channel in the case of men, who also have an acid gastric juice? Certainly they have it no longer when they are suffering from cholera, but they had it up to that time.

When we introduce the agents, that are supposed to generate cholera, directly into the duodenum, the action of the bile being suppressed by means of a ligature around the bile-duct (Nicati and Rietsch), accidents are produced which resemble those of cholera; and as it is found at the postmortem examination of cholera patients that the gall-bladder is distended, and that there is no bile in the intestine, the development of cholera in man is attributed to the suppression of the biliary secretion. But it is because the patient has cholera that we find in him the biliary secretion suppressed. After examining all the theories that have been expressed and all the experiments that have been made, I arrive at the conclusion that the proof of the transmissibility of cholera to animals is still wanting; these have been caused to die sometimes from peritonitis, from septicæmia, or from poisoning, but not from cholera.

# LECTURE XXIX.

## CHOLERA (*Continued*).

**Objections to the pathogenic value of the comma bacillus. Introduction o microbe by the hypodermic method; M. Ferran's inoculations. Experim researches relating to the value of the comma bacillus. Intestinal antis treatment does not prevent choleraic accidents. Search after a poiso the discharges of cholera patients, in their tissues and their secretions. Intravenous injection of the urine of cholera patients into animals r duces most of the symptoms of cholera.**

IN the critical examination which I have made of pathogeny of cholera I have examined the claims of Koch's cillus, and I have found various objections calculated to le the confidence that might be felt with regard to its importa The only argument of any weight in favor of Koch's opinio the presence, in the second part of the intestines of those tacked with cholera, of special organisms not found in the in tines of healthy people, nor in those of patients suffering fr other diseases; it is, in fact, the presence of these organisms fr the very commencement of the choleraic attacks, often in c siderable quantity and sometimes to the exclusion of all ot microbes, in the alimentary canal. With the exception of t empirical fact, which only leads to a hypothesis, all the ar ments brought forward are misleading.

The demonstration to be desired was to obtain the suspec organism in a state of purity, and by its introduction int healthy body to reproduce cholera. It was thought that t experiment could only be tried on animals. Now, animals not contract this disease. They have always, both spontaneou and experimentally, resisted the influence of choleraic dischar introduced directly into their bodies. Could it, then, be expec that cholera would be communicated to them by means of cultivated germs? It seemed highly improbable; but, nevert less, attempts have been made to realize this result by distorti nature, so to speak.

Experimentalists endeavored to get rid of whatever mig protect the animal against the action of the cholera germ, vi the gastric juice, the bile, and the intestinal movements. They rendered the gastric juice alkaline, they conveyed the organism supposed to be pathogenic directly into the duodenum, and they introduced into the peritoneum as much as 5 grams of tincture of opium per kilogram of the animal. The results obtained were various. Sometimes death ensued, but more often the animal survived. When death occurred, it was generally from peritonitis or septicæmia. No results calculated to convince us of the truth of the theory were obtained; only Messrs. Nicati, Rietsch, Koch, Ferran, and Van Ermengen are convinced. Others, even M. Cornil, who still holds that the comma bacillus is really the cholera bacillus, make formal reservations with regard to the subject of the experimental reproduction of cholera.

These results, which I consider negative, do not, however, prove that Koch's bacillus is not pathogenic. They only prove that animals, which are, as we know, refractory to the action of choleraic matter, also resist the cultivated descendants of the microbes which it contains. But is it the same with man? He contracts cholera spontaneously. Is he then attacked with symptoms of cholera when the comma bacillus is developed in his system? We cannot quote any experiment of importance in answer to this question. We may mention the experiments of Bochefontaine, who swallowed pills containing choleraic discharge: he experienced nausea and even vomiting. He inoculated himself in the cellular tissue with the liquid in which the germs were cultivated: inflammatory swellings resulted, but there was no sign of the general symptoms of cholera. The first experiment must not be considered absolutely convincing. The bacilli might be absent from the matter introduced into the system, or they might be in a very small quantity, or the mode of administration might have neutralized them. The second method cannot be appealed to, as cholera is not contracted by hypodermic inoculation. All that we know goes to prove that the infectious agent is introduced through the digestive channels.

This mode of inoculation has been repeated by M. Ferran. He obtained the local phenomena experienced by Bochefontaine, —local septic action in the tissues, rarely terminating in suppuration. I do not know what value may be attached to these inoculations from a prophylactic point of view.[1] But I can see already objections to his methods of procedure. In any case, as far as man is concerned, the facts obtained by experiment do not enable us either to admit or deny the theories of Koch with regard to his bacillus; but, experimental proofs being wanting, observation may, in a roundabout fashion, lead us to certain conclusions.

Before the period when I had to treat cholera patients in the last epidemic I had for a long time reflected on what course I should adopt if cholera did break out. I had seen that the results of physiological treatment were absolutely *nil*, with the exception of intravenous injections. On the other hand, I knew the uselessness of all empirical modes of treatment. Opium, alcohol, etc., have given the same statistical results. I was thus justified in making an experiment in pathogenic therapeutics at the time when a new doctrine gave us the hope of defending the patient against the parasitic germ that was supposed to menace his life.

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[1] At the time this lecture was delivered we had no definite information to enable us to form an opinion on the experiments of Ferran. It could only be said that the principle of his method, if there was any principle in it, had not been proved so far as cholera was concerned. The attempt to create a sort of immunity from a disease by simply changing the mode of introduction of a microbe is a principle that was known before M. Ferran's time. Messrs. Arloing, Cornevin, and Thomas were the first to demonstrate it, in their splendid experiments on symptomatic charbon. But what is true of one pathogenic agent of disease may be false as regards another, and we should therefore, in this case as in all others, guard against hasty generalizations. Unfortunately, the importance of the results announced by M. Ferran is considerably diminished by the report of the French Commission, composed of Messrs. Brouardel, Charrin, and Albarran. This report shows us that M. Ferran was not able, or, at all events, not willing, to give proofs of what he had advanced, both as regards the morphology of the comma bacillus and the effects obtained from it upon animals. The phenomena observed in persons inoculated in no way resemble those of a slight attack of cholera, as the Spanish physician asserted; their blood never contains any of the bacilli. Moreover, M. Ferran refuses to explain the composition and preparation of his lymph, or, if he gives an explanation, he abandons it a few days after for another. Last, the statistics that he publishes, although numerous, are far from being unassailable. In short, the scientific value of M. Ferran's method has not yet been proved. This is the verdict pronounced by the French Commission, and we must own that this verdict has been in no way weakened by the later reports of the other Commissions (Belgian, American, Italian, and Spanish) that were sent to Valencia for the same purpose.

Accepting, therefore, the theory of Koch provisionally, everything seemed to indicate that antiseptic treatment adapted to cholera was the path to follow. If we were dealing with an agent of infection that was scattered through the blood and the tissues, all idea of antiseptic treatment would have had to be given up. But we had before us a doctrine that asserted, authoritatively, arguments that were capable of misleading. I therefore applied the doctrine of Koch to the therapeutics of cholera in all sincerity and good faith. It may be summed up thus: Cholera is produced by a poison formed by organisms in the intestinal canal; it is an infection of an accessible surface. We were able to destroy by antiseptics other microbes in the alimentary canal. Therefore, if Koch was right, it was necessary to introduce into the alimentary canal a substance capable of destroying life in all the microbes,—a nonabsorbable and, consequently, an insoluble substance. I was led to proceed in cholera as in typhoid fever. I employed iodoform in such a state of division that the dose employed represented a surface of sixty square meters; I gave 1 gram a day in conjunction with 5 grams of naphthalin,—a substance that is almost insoluble. I have had a mortality of 66 per cent.,—*i.e.*, equal to that of the other hospitals. This is not a very gratifying result, but we may learn something from it.

What objection can be raised to the accuracy of the following proposition: "If the pathogenic organism exists in no other part of the system, and if we have succeeded in destroying it in the intestines, choleraic accidents ought not to be produced?" In the first place, it may be urged that Koch's microbe is not influenced by iodoform or by naphthalin. This resistance would be surprising on the part of an organism that is more vulnerable than most of the known microbes, since it is killed by heat and desiccation. Moreover, I may mention an experiment made by M. Chantemesse, who checked the germination of the bacilli by introducing into the substance about to be used for their cultivation a small quantity of the preparation administered to the patients.

It may also be said that the treatment was instituted too late, the morbid poison being already formed and absorbed. I answer by facts. A certain number of the patients subjected to the antiseptic treatment recovered. I continued to give them iodoform and naphthalin; several of them had a relapse. Now, these had ceased to be influenced by the poison absorbed at first. A fresh germination must, therefore, have taken place in the system of infectious agents that had remained in some part of the organism, but not in the alimentary canal, the latter having remained aseptic. I conclude from this that the germination of the pathogenic agent of cholera does not take place in the intestines.

While I was attending the cholera patients, I also attended typhoid patients in other wards. The latter having been subjected rigorously to iodoform and naphthalin, their intestines were aseptic, and yet two of them took cholera in the course of typhoid fever, and their evacuations consisted of black matter having only the odor of naphthalin. We have, therefore, two series of facts proving that cholera cannot be a surface infection seated exclusively in the intestinal cavity. The alimentary canal is, in all likelihood, the channel through which the infectious agent enters, this entrance being probably effected through the stomach rather than through the intestines; but it is not in the alimentary canal that the multiplication of this organism takes place.

If Koch's theory is undermined, it is only in one of its claims. I do not say that the bacillus is not the pathogenic agent, but I think that, if it is, it must exist elsewhere than where Koch has seen it. Other investigators believe that they have succeeded in staining it, and in finding it in various organs; they have obtained cultures with fragments of the viscera. Whether the infectious germ in cholera is Koch's bacillus or any other, one, at any rate, must exist; and we should not be justified in denying its existence simply because we have not seen it. The microbe of hydrophobia, which we cultivate in animals and which we can attenuate or intensify, has not yet been discovered. We may, therefore, proceed, notwithstanding the absence of direct demonstration concerning its nature, and admit, in the interest of both prophylaxis and therapeutics, that cholera is an infectious disease. But, granting that there must be a certain pathogenic agent in cholera, let us ask ourselves if this agent does not produce some substance, and if it does not kill by causing a kind of poisoning. This idea, which I formulated in 1879, speaking of infectious diseases generally, has been taken up by Klebs and Koch, in connection with cholera. It would be necessary to show that there exists in the bodies of those attacked with cholera, or in their excretions, a particular toxic substance, capable of reproducing in other living beings symptoms similar to those of cholera.

M. Gabriel Pouchet has discovered the existence of an alkaloid in the discharge of cholera patients, and M. Hayem also mentions one. It would have been more satisfactory if they had stated whether these were particular alkaloids distinguished from those which are found normally in the fæcal matter of both the sick and the healthy.

Even before these discoveries, on September 20, 1884, in the case of a ragpicker suffering from cholera, one of that little group of individual cases that formed the local epidemic of Saint-Ouen, the forerunner of the true Parisian epidemic, I found, in an extract of 575 cubic centimeters of intestinal matter, a considerable quantity of an alkaloidal substance,—a quantity which certainly exceeded the proportion of alkaloids generally contained in fæcal matter. This alkaloidal substance differed from the other intestinal alkaloids in one of its chemical characteristics. If, like them, it was precipitated by the iodo-iodurетted reagent, by the iodides of mercury and of potassium, by the phosphomolybdate of soda, by tungstate of soda, it did not present the reaction with tannin. During the epidemic of November, 1884, I found this alkaloid again with the same characteristic. I also saw it crystallized in the form of long and extremely fine needles; but I was not able to experiment upon its physiological characteristics, not having been able to obtain a sufficient quantity of it. For this reason, I thought it best to leave the report of these observations among my laboratory notes.

Another question arises as regards this alkaloid. Supposing it to be a substance peculiar to cholera patients, might it not have been produced in some other way than by the action of parasitic organism? I know that in cholera patients matter is formed differently from that in other people, whether ill or in good health. Speaking of this, I may mention a peculiarity in connection with naphthalin. All my patients were treated with this substance. In some it underwent normal metamorphoses. In others it underwent unusual metamorphoses, which I have also remarked in acute yellow atrophy of the liver and in two cases of typhoid fever. In these latter cases, the urine, instead of retaining the somewhat dirty, blackish-brown tint which it assumes in people that have been subjected to naphthalin, assumed spontaneously, at the moment of emission, a deep-violet color, like that of a solution of permanganate of potass. It was not the pink tint that is generally obtained by means of acetic acid in the urine of patients who were being treated with naphthalin. The violet matter in choleraic urine is soluble in ether, whereas that which appears upon the addition of acetic acid in the urine of other patients treated with naphthalin will not dissolve in ether. This anomalous fact is probably owed to certain changes in the liver. Other substances besides naphthalin might, therefore, be as irregularly transformed, and certain anomalous substances found in the passages or in the alimentary canal of cholera patients may have been generated in the liver or in the system without the intervention of microbes. There are, besides, in cholera patients, special toxic substances, which cause death in a different manner to the normal poisons of the system. There is a choleraic poison which is shown by the special toxicity of the urine of cholera patients. The experimental injections of the urine of cholera patients rarely produce in animals the symptoms of poisoning by normal urine.

Myosis is generally defective. Instead of appearing at the tenth cubic centimeter, it comes later or is absent altogether. But one sign is very soon observed, which is not produced by injections of any other kind of urine,—cyanosis, which is shown on the inner surface of the ear in the rabbit; then muscular cramps, which in no way resemble the convulsions produced by other kinds of urine, being spasms which begin long after the commencement of the injection and continue for half an hour after it has ceased. They consist of a slow and protracted stretching of the hind limbs, followed by four or five spasms at the end of a minute and a half, another rigid extension of the limbs, and fresh spasms; eight, ten, or fifteen similar contractions may take place, and then quietness is restored.

Cooling of the surface is more marked after the injection of choleraic urine than with normal urine. Albuminuria appears at the commencement and is intense, whereas it is rare and does not appear till late with normal urine. After the injection of normal urine the animal is restored to health; after the injection of choleraic urine the animal is seized with pea-soupy diarrhœa, the motions being pale or reddish, without any trace of bile. The albuminuria goes on increasing; then, after a day and a half, anuria sets in, the *refrigeration* continues and becomes more marked, and the animals die, with a rectal temperature of 33° or 34° C. On the bodies being examined, the intestine is found to be congested and filled with pea-soupy, diarrhœic matter, constituted mainly by the intestinal desquamation, resembling choleraic diarrhœa so much that it might be mistaken for it, except that no bacilli are found. Either the urine injected was infectious, or we had obtained a form of poisoning similar to that determined by the infectious agent in cholera when it has produced toxic material.

# LECTURE XXX.

## CHOLERA *(Conclusion)*.

**A special poison exists in the urines of cholera patients. The symptoms of the animals into which they are injected cannot be explained by infection. Effects produced on animals by the substances soluble and insoluble in alcohol and contained in choleraic urine. The poison which causes the choleraic symptoms in animals in soluble in alcohol and is organic. The second period in cholera is the result of a fresh intoxication occasioned by the normal poisons, from which the kidneys no longer free the system: it is uræmia. Myosis in cholera patients that are anuric. This terminal uræmia in cholera differs from ordinary uræmia, as several of the sources of the uræmic poisons are suppressed. The toxins of cholera. Brunton, Roger, Besson. Treatment of cholera.**

THE history of the progress of cholera compels us to look upon it as an infectious disease. But it is doubtful whether Koch's pathogenic agent is the true one. Admitting, from analogy, that there is an infectious agent peculiar to cholera, we must ask ourselves whether the microbe is responsible for all the ill effects observed, or whether, among the symptoms of the illness, there may not be toxæmic accidents, attributable to a substance formed by the system itself, or by the microbe.

I believe that this poison really exists, and the study of the toxic nature of the urine in cholera patients has led me to think that it is eliminated by the urine. The toxicity of choleraic urine presents special characteristics. Besides the properties which it has in common with normal urine (pupillary contraction, weakening of the muscles, certain respiratory disturbances, fall of temperature, and diuresis) choleraic urine produces, in the animals into which it is injected by the intravenous method, very marked cyanosis on the inner surface of the ear,—a much greater fall of temperature, lasting until death takes place; cramps, which I have never observed with injections of other kinds of urine, and which are very different from opisthotonos and convulsions,—cramps which consist of a long, slow extension of the limbs, which is repeated at short intervals for half an hour; diarrhœic evacuations, which may occur with certain normal or pathological urines as with distilled water, but in this last case only with enormous quantities of urine, whereas a very small quantity of choleraic urine produces motions of a whitish, yellowish, grayish, or reddish color, the coloring being due to epithelial desquamation of the small intestine and to the retention of bile in the gall-bladder.

Albuminuria, which is rare and very slight with normal urine, is in this case always considerable or intense, lasting throughout the experimentally produced disease. This albuminuria may be succeeded at the last by complete anuria. At length death ensues,—not during the injection, but after an interval of from twelve hours to four days; whereas with animals whose death is caused by the injection of other normal or pathological urine death occurs always during the injection. With choleraic urine nearly all animals die; in those that survive we may follow the development of the disease. The thermometer indicates the gradual return of heat production; the appetite does not return for some time, the albuminuria diminishes, and complete recovery is not effected until after about six days.

In what light are we to consider these accidents? Are we dealing with a case of infection or of experimental poisoning? I have answered some of the suppositions that might be made. To account for infection, the infectious agent must have been in the urine of the patient; discharges containing bacteria must have come from the kidneys. Now, we do not find any microbes in the urine of cholera patients, either by direct examination or after coloration. It is true that, in several diseases which are evidently virulent, we cannot find microbes (hydrophobia, for instance), or we can only demonstrate their existence by improved methods of coloration (as in tuberculosis or leprosy). Thus, there are microbes which remain invisible to us; the cholera germ is perhaps one that calls for a special technical treatment in order to be discovered.

We might have tried to obtain cultures with the urine of cholera patients. I have not tried this, as I was only able to obtain the urine of female patients; and in their urine one is always liable to meet with some of those agents of infection which germinate readily on the external genitals, the conditions of temperature and moisture being very favorable to their development. But these means were not required in order to settle the question. If the disease that we communicated to animals by intravenous injections of choleraic urine had taken the course of an infectious disease, we should have to acknowledge the existence of a phase of incubation which was altogether absent. We saw all the symptoms appear immediately after the introduction of the urine and continue their course without any interruption. This total absence of incubation is a decisive argument. Moreover, if the disease that we produced was of an infectious nature, the quantity of urine injected would be of little importance; the infectious germs, by their multiplication, would always produce the same symptoms, whatever the quantity of choleraic urine introduced into the system. Now, this was not the case: we always observed an exact proportion between the quantity of urine injected and the gravity of the disease.

Two animals survived, having been subjected to an injection of only 12 cubic centimeters. All of those that died received more than 17 cubic centimeters, and some as much as 90 cubic centimeters. From the two reasons given above, I conclude that the experimentally produced disease resulting from injections of choleraic urine is of a toxic nature.

I evaporated all the water from some choleraic urine and obtained, by the processes that I employ with normal urine, two extracts,—one containing the substances that are soluble in alcohol, the other those that are insoluble in alcohol. I poisoned some animals with these two extracts, but the results observed were not the same in both cases. After the injection of the alcoholic extract of normal urine we observe salivation, coma, and death, if the quantity injected is sufficient; if not, the animal is restored to health in less than half an hour.

With the alcoholic extract of choleraic urine we rarely obtain salivation; we sometimes get somnolence, but the animals do not recover. They have albuminuria and diarrhœa, and die within two days. These last accidents—albuminuria, colorless diarrhœa, and death in two days—are the same as those produced by the injection of choleraic urine itself. But I did not obtain cyanosis and cramps with the alcoholic extract alone.

With the aqueous extract containing the substances that are insoluble in alcohol I observed, as with normal urine, myosis and, when the quantity was sufficient, convulsions; but these last in no way resembled the spasms produced by the urine of cholera patients. Last, in order to produce death, larger quantities of the aqueous extract were required than of the choleraic urine itself. When death occurred, it was always immediate, never delayed. I never observed either albuminuria or diarrhœa, and all the animals that survived were restored to health after this short toxic illness of half an hour's duration.

Thus, there exists in choleraic urine something which is carried off by alcohol, and which is different from the substances generally found in urine,—something which can be separated from the other parts; in short, a special morbid poison. In regard to the toxic accidents caused by the alcoholic extract of choleraic urine we note the absence of cramps. Are we mistaken in attributing them to the cholera poison? Besides the special features belonging to cholera poisoning, might not the cramps be caused by the substance that gives the urine its convulsive property, viz.: potass? But choleraic urine produces cramps at 17 cubic centimeters per kilogram of the animal. I evaporated 400 cubic centimeters of choleraic urine; the extract was reduced to ashes and the residuum washed in distilled water, which carries off all the potass. Now, the whole of the aqueous liquid obtained was injected little by little, without producing any toxic phenomena or convulsions.

Thus, there is in choleraic urine a poison which is a soluble organic substance, and which I call the choleraic poison. I cannot either name or define this poison chemically; I only know it by its physiological properties. I do not know whether it is formed by the diseased organism carrying on the work of elaboration defectively, or by microbes,—whether it is produced by the patient himself or by the vegetable parasites that have caused the disease.

I cultivated in my laboratory Koch's comma bacillus. I had at my disposal a considerable quantity of pure culture liquid, and I endeavored to solve the two following questions: 1. Does the comma bacillus determine in the liquid the formation of a toxic substance? 2. Does the comma bacillus really possess a special pathogenic property,—*i.e.*, does inoculation with it produce in animals the appearance of cholera?

In order to answer the first question I made several experiments. I inoculated by the subcutaneous method some guinea-pigs, weighing on an average 550 grams, with from 3.8 to 35 cubic centimeters of the undiluted liquid in which comma bacilli had been cultivated. These animals experienced no morbid symptoms. In the second instance I introduced under the skin of another guinea-pig, weighing 575 grams, 20 cubic centimeters of the liquid heated to 63° C. Neither at the time of the inoculation nor after it did the animal seem affected in any appreciable degree. Proceeding with the solution of this first question that I had asked myself, and wishing to employ the intravenous method, I experimented on a rabbit. I injected into the veins of the ear of a rabbit, weighing 1800 grams, 79 cubic centimeters of the culture fluid, which had neither been heated nor filtered from the bacilli,—that is, 43 cubic centimeters per kilogram. At the moment of the experiment the only effect shown by the animal was accelerated respiration, especially at the end of the injection. It died twenty-four hours afterward. The postmortem examination showed pulmonary congestion, slight diarrhœa, somewhat intense albuminuria, the absence of comma bacilli in the excrement, and the presence of some of these bacilli in the kidneys, to which the blood, having received, had conveyed them. Altogether, the symptoms observed, and especially the interval of time that elapsed between the injection and death, suggested infection, and not poisoning. Last, another rabbit, weighing 1990 grams, received into the veins of its ear in five minutes 92 cubic centimeters of the liquid, which had been heated and filtered from the bacilli, or 46 cubic centimeters per kilogram. The temperature fell $^{8}/_{10}$ degree at the moment of the experiment, but the animal showed no other sign of disturbance, and it afterward continued in good health. These experiments, which I describe briefly, enable me to dispense with long arguments. They fully justify me in giving a negative answer to the first question: the liquids in which the comma bacilli are cultivated contain no substance of a toxic nature.

In order to answer the second question—as to whether the comma bacillus is capable of producing cholera in animals—I experimented, like Koch, on guinea-pigs. As Koch did, I introduced into the stomach of my guinea-pigs 11 cubic centimeters of the liquid, after having first, according to the German scientist's method, alkalized the stomach by means of 5 cubic centimeters of a 5 per cent. solution of carbonate of soda, and arrested all motion in the intestine by the intraperitoneal injection of 3 cubic centimeters of tincture of opium. I must own that the results I obtained were the same as those secured by Koch himself. My guinea-pigs soon died. After death I found that the stomach was in most cases dilated, that the small intestine contained, more or less abundantly, diarrhœic matter, and that there were comma bacilli, in varying quantities, to be observed in this material. But I also instituted other experiments: with some other guinea-pigs I alkalized the stomach and checked the action of the intestine exactly according to Koch's method and as I had done in the experiment just described. But in this second experiment, instead of using the same kind of liquid as before, I introduced into some of the guinea-pigs 11 cubic centimeters of an old charbon culture-fluid and into others 11 cubic centimeters of liquid that had been turned acid by exposure to the air, or some old pyocyanic culture fluid. Well, the animals died almost as rapidly as those that had received the comma bacilli, presenting almost the same symptoms, except that the diarrhœa was less abundant. These last results singularly detract from the value of the first series of experiments; and, without denying that the common bacillus has any pathogenic property, we are, in my opinion, justified in asserting that this pathogenic property has not yet been clearly demonstrated.

If, then, judging by its analogy to other infectious diseases, and by the history of its migrations and of its localized centers, I am led to admit that cholera is caused by infection, I am also justified in saying that, side by side with the infection, there exists in the pathogeny of cholera a secondary poisoning consequent upon infection. I think that the symptoms which are considered characteristic of cholera, and which enable us to form the diagnosis, are the results of this poisoning. It is to this cause that we must attribute cyanosis, refrigeration, respiratory disturbance, hiccough, the peculiar form of diarrhœa, intestinal desquamation, cramps, dehydration of the tissues, albuminuria, and anuria. These are the symptoms of cholera poisoning, and I may add to the list the preservation of consciousness and the absence of pupillary contraction.

But soon a second poisoning supervenes, which is associated with the first or alternates with it; it takes the clinical form of mental torpor, loss of consciousness, somnolence, and coma. The respiratory rhythm changes; it becomes that of uræmia, or what is known as Cheyne-Stokes' respiration. The temperature is affected, sometimes rising and sometimes remaining low. At the same time the pupils contract and become punctiform.

Is not this series of symptoms very different from that of the earlier period; and does it not, therefore, spring from another kind of poisoning? We observe all these symptoms when anuria and myosis appear, and they are all to be found in the clinical picture of uræmia. Among authors I have not found any indication bearing upon this fact. I was myself ignorant of it until the day when this coincidence between the suppression of the urinary secretion and the appearance of those symptoms, the existence of which I knew to be in uræmia, stood clearly out before me.

This uræmia of the second phase of cholera is not the ordinary uræmic intoxication by poisons produced from four sources; we cannot in this case attribute it to alimentation, or to intestinal putrefactions, or to biliary reabsorption, since there is no jaundice at the time, and the absorption cannot be effected by the intestine. The poison in this case comes from disassimilation. This uræmic period has long been designated the period of reaction, the external temperature being higher,—*i.e.*, equilibrium being established between the rectal and peripheral temperatures,—a singular reaction, in which torpor appears instead of spasms, and in which we can only see inertia of the whole nervous system! It is a perversion of the meaning of the word to apply such a name to this phase of the disease. It has also been termed the typhoid phase, and the period of typhoid reaction,—a designation that is certainly less open to criticism, for in the condition of the patients there is certainly something that reminds us of typhoid fever. But the pathogenic conditions are not absolutely the same. In cholera patients whose intestines are subjected to antiseptic treatment there is no intestinal putrefaction; they experience poisoning by disassimilation only. It was therefore asserted that this phase of cholera must be considered a uræmic period. There was no need to wait for pupillary contraction in order to detect signs of uræmia; the blood and the tissues were analyzed, and extractive matter and urea were found accumulated in them in considerable quantities (1.20 grams and 1.30 grams of urea per kilogram of muscular tissue). This period can be foreseen when anuria sets in; after pupillary contraction it can be affirmed. In all patients seized with anuria myosis occurs; I have observed it in every case; this is a clinical fact which, in my opinion, is of some importance.

If we do not find in the uræmia following cholera all the symptoms usually observed in ordinary uræmic poisoning, it is because several of the sources of the uræmic poisons are suppressed. Disassimilation may supply the narcotic poison as well as the convulsive poison. When potass is sent into the blood in excess it causes convulsive uræmia; but if convulsive uræmia is not generally observed in the uræmic phase of cholera, we can understand why not. The rapid and premature dehydration has drawn off with the water all the potass of the fluids and a portion of that in the anatomical elements; thus, when the period of excessive destruction of matter arrives, potass and mineral substances are not so superabundant in the blood as organic and extractive substances. In a case that I have already quoted, there was so little potass that an extract of 400 grams of the patient's urine did not cause convulsions in an animal. We see that cholera furnishes us with an example of double self-poisoning: first, by an anomalous product (this is cholera poisoning, properly so called); second, by normal products (this is a variety of uræmic poisoning). Moreover, the study of cholera corroborates the theory that anomalous substances may exist in some diseases, and that morbid poisons are not a dream.

[Bouchard in discussing the subject of cholera in the three preceding chapters shows by the questions he has raised and answered that the pathology of the malady is far from regarded as settled. Although Asiatic cholera is usually attributed to the spirillum discovered by Koch in 1883 there is a growing opinion that it is due not so much to the bacillus itself as to the absorption of a toxin formed in the intestine by the micro-organism. In his book "On Disorders of Assimilation and Digestion," page 267, Sir Lauder Brunton states that the symptoms of cholera are identical with those caused by muscarine, an alkaloid obtained from poisonous mushrooms; hence his suggestion of the employment of atropine as an antidote. Albuminous matter, in decomposing, gives birth to such poisons as cholin, neurin, and muscarine. Roger, in "Les Maladies Infectieuses," page 175, speaks of the cholera poison as a toxopeptone, while Gamaleia regards it as a very unstable form of nucleo-albumin contained in the body of the cholera bacillus. From cultures of this organism there is recovered a protein or nuclein which resists heat and which kills animals with all the symptoms of cholera. In "Technique Microbiologique et Serothérapique," by Besson, on page 511 it is stated that Petri found those cultures the most toxic that were grown in a 5 to 10 per cent. solution of peptone and that the toxin thus prepared was extremely fatal to guinea-pigs and was not destroyed by boiling: a point of difference between it and the diphtheria toxin, which he also named toxopeptone. Brieger and Fränkel regard the poison as an albuminoid of an indeterminate nature resembling diastase and which is called by them toxalbumin.

The symptoms of cholera can be caused by the comma bacillus of Koch, but Bouchard, Brunton, and others are of the opinion that this bacillus has not the monopoly of producing the malady. Gautier, "Les Toxines Microbiennes," page 581, holds the opinion that there are various kinds of cholera microbes,—*e.g.*, the bacillus of Asiatic cholera (Koch, Haffkine), the bacillus of Hamburg cholera (Pfeiffer), that of Massowah and Cassino. From a specially prepared culture of Koch's bacillus there is obtained a product composed of proto- and deutero- albumose. This is toxic and is capable of producing immunity against fatal doses of the cholera microbe. D. D. Cunningham failed to determine the presence of Koch's bacillus in the dejecta of cholera patients, but he found 11 other kinds of micro-organisms therein. Several other physicians, therefore, as well as Bouchard, maintain that, although the comma bacillus is the micro-organism that is most frequently present in cholera, other micro-organisms can replace it, and since the injection of poisonous substances obtained from the stools of cholera patients is followed by symptoms of the disease it would appear as if the malady was due rather to the absorption of a toxin formed by bacilli present in the intestine than caused by the circulation of bacilli in the blood or their presence in the tissues of the body. Whatever may be the nature of the poison, and we have seen that opinions differ very much in regard to it, there is in all probability required a preparedness of the soil or a receptivity of the individual upon which the poison can act.

The treatment of chŏlera should be twofold: *(a)* antiseptic, to destroy the bacillus in the intestine and *(b)* the use of remedies to neutralize the poison formed by the micro-organism. As antiseptics, Brunton recommends the internal administration of liquor hydrargyri perchloridi, ♏xv to ʒj, with or without small doses of calomel and as an antidote the internal administration of atropine. Since the toxalbumins of cholera, when injected subcutaneously, are excreted by the mucous membrane of the stomach, from which cavity they may be reabsorbed into the system, lavage is well worthy of a trial.]

## LECTURE XXXI.

### THE GENERAL THERAPEUTICS OF SELF-POISONING.

**The course to be pursued is to prevent the poisons being formed; to oppose their penetration into the system; if they have been absorbed, to try to destroy them or to stimulate the action of the liver, which is a physiological destroyer of poisons; last, to encourage the elimination of poisons by the skin, the lungs, the intestines, and the kidneys.——Sudorifics, purgatives, diuretics, bleeding, inhalations of compressed air and oxygen; intravenous injections of antiseptic remedies.**

IS IT possible to make any therapeutic application of the knowledge that we have acquired with regard to the pathogeny of self-poisoning? The first course to take is to prevent the poison being formed. When once it is formed, we must endeavor to oppose its penetration into the system by preventing its absorption. This can be realized in certain cases; certain toxic substances are naturally precipitated in the intestines, and others may be fixed by charcoal, which retains them physically. If the poison has been absorbed, we must endeavor to destroy it. We have found that the liver has the power of arresting poisons; it withdraws them from the intestine and eliminates or destroys them. We should therefore stimulate its action by certain therapeutic treatment. Last, if the poison has escaped the action of the liver it should be eliminated by the skin, the lungs, the intestines, and the kidneys.

If all these attempts should fail, we must have recourse to certain antidotes which tend to counteract the physiological effects of the poisons that menace the system. We have a striking example of the antagonistic properties of poisons in atropine and pilocarpine. This side of the question has so far merely been sketched out. We have, however, indicated, from a pathogenic point of view, the existence of poisons that are allied or opposed to one another; in poisoning by substances in the urine, I have shown how the action of the narcotic material prevents that of the convulsive poisons. The knowledge of these facts shows us, at any rate, that we should not give up the contest. In any case, we must never neglect, in auto-intoxication, to keep up the strength of the patient, so that he may have time to eliminate the poison. Sometimes we only require to keep him alive a few minutes more in order to save him; we cannot supply him with radical force, but what he requires is active force. Thus we are led to administer not tonics, but stimulants, which may awaken some force remaining latent.

The therapeutic treatment is effected, to a certain extent, by nature, or a portion of it is carried out by our organs; in uræmia, one of the sources of poisoning is already lessened, disassimilation being checked by the disease itself in uræmic and other patients attacked with self-poisoning. Poisoning by substances of alimentary origin may be diminished. If potass really kills, the diminution of solid ingesta diminishes the poisoning; now, these patients still drink, but no longer eat. They must not take broths which contain the mineral elements of meat. The poisons of the secretions are opposed to each other, both naturally and physiologically. The system itself exercises prophylactic action. The bile which is not eliminated by the intestine is precipitated. Of the poisons which it contains one, which is eminently poisonous,—the coloring matter,—is precipitated when brought into contact with acid chyme; the other—the biliary salts—is transformed and brought to the condition of dyslysin. In this way man lives, thanks to the therapeutics which the system exercises incessantly upon itself.

The substances which are generated in the intestine by putrefaction, and which are neither precipitated nor eliminated, pass on into the blood; but a natural effort to stop them is made by the liver, which partly prevents them from penetrating into the general circulation. From this point of view, there is a great difference between poisoning through the digestive channels and that which is effected by intravenous or subcutaneous processes. I know a patient who takes daily 20 grams of laudanum without ill effects. Is this because the poison is eliminated through the urine? If so, this should be poisonous. But it is not; it kills only in the proportion of 64 cubic centimeters per kilogram. I might conclude that the poisons of the opium have been destroyed, but in stating this conclusion I must make the most express reservations, for a rabbit shows itself almost as refractory to intoxication by opium as to poisoning by belladonna. In my opinion, the reason why this patient has not been poisoned is because I have introduced the poison through the intestine. I must remind you of the facts observed by Schiff with regard to the protective function of the liver,—facts which Messrs. Charrin and Roger have recently verified in my laboratory. But still the true protecting agent of the system is the kidney.

If I have once more returned to the many physiological actions which tend to neutralize and expel poisons, it is in order to show more clearly how therapeutic treatment may complete the task of deliverance commenced by the system. As far as the alimentary canal is concerned, I have shown that we can expel the contents of the intestine, precipitate with charcoal and fix certain poisons, and even suppress the formation of poisonous matter by instituting intestinal antiseptic treatment.

I have mentioned bleeding, which can carry off in one operation, by the abstraction of 32 grams of blood, more poisonous matter, it is said, than 100 liters of perspiration. I have sketched out the physiological compensations for the action of poisons that can be obtained by the help of chloroform, chloral, bromide (of sodium), diffusible stimulants, alcohol, and injections of ether.

In most diseases the morbid poison is a natural one, and the ataxic or adynamic accidents of pyretic diseases are the consequence of febrile oliguria; these are auto-intoxications resulting from more intense disassimilation, or from more rapid cell destruction, which sets at liberty imperfectly oxidized nitrogenous matter and an excess of potass. We should, therefore, by stimulating the renal discharge, hasten the elimination of this excess of poison that has been sent into the circulation.

In cases which are certainly more rare, but the number of which will be increased perhaps when we shall have penetrated further into the secrets of the pathogenic processes, in cases where a morbid poison is really formed by perversion of the nutritive functions, we must endeavor to prevent the formation of this poison. If it is formed in the tissues, will this be possible? It has always, up to now, been said that we cannot act upon poisons which have impregnated the system. But, in the first place, without speaking of poisons of interstitial origin, there are those which may be formed on accessible surfaces. Already, in some cases, we are able to effect a rapid cure of the suppuration in abscesses, fistulæ, and empyemata.

We know how to encourage the elimination of the poison, and to prevent its continuation by drainage, washing, and the attitude in which the patient is placed. We draw off mechanically the putrid products, and contend against putrefaction in the accessible natural cavities,—the vagina, the uterus, and the intestines. In such cases antiseptic remedies bring about an improvement at once: a sudden fall of temperature, a diminution in the dryness of the mouth, and alterations of the cardiac rhythm. In diseases caused by eating bad food, in severe putrid diarrhœa, provided that the treatment is instituted before the occurrence of secondary accidents and the establishment of metastatic centers, we can really effect a cure; but, if we have not succeeded in preventing the formation of poisons, we cannot depend upon the protection of the liver, unless it is interposed between the source of the poisons and the other organs. This condition only exists in poisoning of intestinal origin. It is true that a portion of the poisons absorbed will pass back into the liver with the blood of the general circulation, but this will only be a very small fraction instead of the whole.

I very much doubt whether we shall ever know that the function of the liver can be stimulated by medicinal treatment, and whether the employment of purgatives, in intoxications that are not produced through the intestines, can thus be justified. In toxæmia from intestinal poisons, the utility of purgatives is explained in quite another way; they expel the poison mechanically.

What can we do against poisons in the circulation? Endeavor to eliminate them. In all ages the course adopted has been to increase the action of the various emunctories of the body. To provoke perspiration was the alpha and omega of the therapeutic treatment of antiquity. Hot or warm drinks, wrapping in hot linen or wet sheets, the administration of Dover's powder have all been employed with the object of acting upon the humors. I am inclined to think that the result of perspiration is not beneficial, since perspiration lessens the urine, which carries out of the system so many toxic products. If in former times it was thought advisable to provoke perspiration, it was not used so much in cases of poisoning in order to eliminate the poison as in cases in which a dynamic action, such as the dilatation of the cutaneous capillaries, might relieve the centers; and when in our own times we have thought it advisable to produce copious perspiration with pilocarpine, we have not found the general condition improved. It is true that perspiration may help to eliminate certain toxic substances, but the true depuration of the system is accomplished chiefly through the kidneys. It is the kidneys that enable the body to be thoroughly cleansed, and this is effected by increasing the renal secretions by cold drinks and cold bathing.

When in typhoid patients the quantity of urine rises from 500 grams to several liters and the result is an improvement, it is very probable that this is owed to the expulsion of toxic matter through the urinary passages. Last, we must not omit the intestinal outlet, which may be acted upon by judicious drastic treatment.

Bleeding is of use only in toxæmia attended with anuria and serious impermeability of the kidneys. Perhaps it is possible to do something more to destroy the poison or prevent its formation. I have told you in what proportions compressed air diminishes urinary toxicity. This may be explained in two ways: either disassimilation, taking place in presence of a greater proportion of oxygen, gives rise to more completely oxidized products, which are less toxic, or the corpuscles, having more oxygen at their disposal, destroy in the blood a greater mass of poison. Hence the utility, which is, perhaps, somewhat theoretical, of compressed air or inhalations of oxygen.

If these methods fail, we can only have recourse to antidotes, the properties of which we have learned empirically; in ataxo-adynamic fevers, opium, musk, and sometimes chloral, which can neutralize certain poisonous effects; diffusible stimulants, alcohol, coffee, injections of ether. Even if the morbid poison is formed by microbes within the organs, we are not justified in saying that it is impossible to oppose its development. At any rate, I have attempted this impossibility. In my trials of general antiseptic treatment, I had to turn my attention to substances capable of arresting life in the infectious agents and rendering the activity of the microbes less intense. I had to adopt the intravenous mode of injection for these substances; for the absorption is so slow by the subcutaneous or intestinal method, and the elimination through the emunctories so rapid, that the antiseptic agent would not have time to impregnate the whole system. Observe that in all that I am saying there is nothing that should at present be applied to the therapeutic treatment of man; but I am justified in seeking, by experiments on animals, the solution of problems which so deeply concern the future of medicine. In order to try general antiseptic treatment by the intravenous method, it was necessary to attack first those diseases in which the microbe exists exclusively in the blood. The objection will perhaps be raised that the pathogenic agents of infectious maladies do not, as a rule, inhabit the blood; this would, however, be to forget recurrent fever, charbon, or malignant pustule. But, to speak only of the infectious diseases of animals, if my attempts failed when directed against Charrin's septicæmia, I obtained some encouraging results when treating bacteridian charbon.

Last year I made out a list of some of the substances that may be utilized for general antiseptic treatment. Of these I will only discuss mercury. For my experiments I chose the biniodide of mercury, the most antiseptic, but not the most toxic of the salts of mercury. The therapeutic equivalent of the iodide of mercury is 2 milligrams. If we exceed this quantity we provoke protracted albuminuria. This quantity is dissolved by means of an equal quantity of iodide of sodium in from 5 to 12 cubic centimeters of water.

I will now give the *résumé* of the trials of general antiseptic treatment that I made with iodine and mercury. The greater number of the animals attacked with bacteridian charbon that I treated with injections of biniodide of mercury died. Nevertheless, when we effected the inoculation of the bacteria not under the skin, but in the blood in the veins, these animals lived longer by several hours, even a day longer. Moreover, when the animals died we no longer found any bacteria in their blood, nor in cultivations of their organs, and the inoculations made with their blood were negative. Why, then, did they die? No doubt because they were not able to bear the double attack of the experimental disease and the treatment; but they no longer had charbon. At length, after a series of failures, one animal recovered, and this animal, on being reinoculated twelve days after, did not contract charbon. This is certainly only one fact, but I may say that it is full of promise, and this single fact enables us to believe that general antiseptic treatment is not merely a vain dream or a therapeutic chimera.

# LECTURE XXXII.

## GENERAL RECAPITULATION.

HAVING arrived at the end of this study of the part played by auto-intoxication in disease, it will be to our advantage to take a rapid survey of the knowledge that we have acquired, and we will therefore devote the last of these lectures to this recapitulation.

We found, in the first place, that disease may spring from four main sources. Man, as we have said, contains in himself the cause of many diseases. His life may not be normal, or, to express the same idea in other words, his nutrition may be defective. This impaired nutrition may have been inherited, or he may be the victim of acquired nutritive disorders. Thus, disease may arise from derangement of the nutritive functions. The human organism may be disordered through external causes, —mechanical, physical, or chemical. To give an example of each of these causes, we may mention bodily injuries, burns, and poisoning. These causes reach the cells directly and provoke their immediate reaction. I must own that this pathogenic process rarely remains in a condition of simplicity, and that often it is rendered more complex by nervous reflex action or by infection. External causes, in fact, may also exercise an indirect influence upon us through the medium of the nervous system; it is through this fresh pathogenic process that the diseases are developed which I have called diseases induced through nervous reactions. Last, our bodies may be attacked by parasites and become diseased through infection.

Poisoning, at its inception, comes under one of these great pathogenic groups; but the other processes—the preliminary disorders of the nutritive functions, as well as nerve reactions and infection—may also act in a secondary manner by intoxication. When nutrition is lessened,—as in obesity and gout, for instance,—we frequently observe certain nerve troubles,—apathy, dejection, inaptitude for work, and headache,—and we generally note in the renal, cutaneous, or pulmonary excretions some incomplete oxidized products of disassimilation,—oxalic acid and the volatile fatty acids. It is admitted, not without an appearance of reason, that these bodies, which are all toxic, are not foreign to the production of these nerve symptoms. They are the very first signs of poisoning due to the previous derangement of nutrition. The same injurious substances, causing similar nervous disorders, may, in people who are in good general health, be produced superabundantly or destroyed insufficiently, owing to excesses, late hours, mental anxiety, or to the influence of dampness, cold, or living in places that are badly ventilated and badly lighted; all of which causes affect the body only by first acting upon either the central or peripheral nervous system. This is another example of the first signs of poisoning due to a pathogenic nerve reaction. Of the substances formed by certain microbes there are some which, even in small quantities, are eminently poisonous. From such substances certain microbes develop putrefactions, which may become the pathogenic agents of certain forms of septicæmia. If, then, the disease is not complicated by injury to important organs; if the microbes do not exist in the blood, the nerve centers, the lungs, the liver, the kidneys, or the heart; if they only exist—suppose it is a case of septicæmia—in the cellular tissue of the region contaminated, it is quite natural to attribute the general symptoms to the absorption of the poisonous matter formed by these microbes, and we can hardly understand that these general symptoms could have any other origin. There are, then, to all appearances, certain cases in which infection leads in a secondary manner to intoxication. Thus, man is poisoned not only when he swallows a poisonous substance or when he breathes a mephitic gas, but also when he is attacked by certain diseases. When the poison is produced by some external cause, or when it is formed in the system by a perversion of the nutritive functions or by the secretion of a microbe, it must be considered as anomalous substance, either as regards its nature or its quantity. But normal poisons exist.

The healthy man, as I have said, is both a receptacle and a laboratory of poisons. In fact, he receives them in his food, he creates them by disassimilation, and he forms them in his secretions. The human body is the theater of the toxic elaborations carried on by the normal microbes which constantly inhabit the alimentary canal. And yet man is not poisoned. He is defended in various ways against poisoning. In the first place, his liver protects him, by arresting on their way, before they pass into the general circulation, the poisons brought from the intestine by the portal vein, in order to neutralize them or throw them back into the intestine. Then the excretory system expels the poisons which are in circulation. This is not a purely theoretical view. I have demonstrated it experimentally, taking the natural product of an excretion and studying its toxicity by injecting it into the veins of an animal.

The traditional idea that normal urine is poisonous had been rejected by Muron; its truth was only established in 1880, by Feltz and Ritter. But they only observed the fact of the toxicity of the urine; they did not pursue in detail the study of the characteristics of the poisoning which results from the introduction of the urine into the veins. I have studied this subject, determining not only the quality, but the intensity, of the urinary toxicity.

I found first what mass of living matter can be killed by the poisons which each kilogram of the body of a healthy man supplies in twenty-four hours to the renal secretion. I thus possessed a standard which enabled me to study the variations of intensity in the urinary toxicity, under certain physiological conditions and under various pathological circumstances.

By varying the experiments I showed that there was not *one* particular urinary poison, but that the urine contains many poisons. Having, by the help of charcoal, acted upon urine with alcohol so as to separate its many constituents, I succeeded in disassociating the various elements of its toxicity, and in showing that it contains at least seven toxic substances: a diuretic substance (urea); a narcotic substance; a substance that produces salivation; one that contracts the pupil; one that lowers the temperature; two convulsive substances,—one of an organic nature, the other a mineral (potass).

It is because all these substances are carried away through the urine that the urine is poisonous, and that man escapes. All these poisons come from the blood; and yet the blood is not poisonous, for it is continually freeing itself from the poisons that flow into it, either by transferring them to the excretory system or to the various organs, or by consuming them when they are brought into contact with the corpuscles. I have just said that the blood is not poisonous; this assertion must not be taken literally. As poisons are continually passing through it on their way to the excretory system, the blood must necessarily contain toxic matter at each moment. The blood, then, has really a toxicity, which may be very slight; the question is, can this degree of toxicity be disregarded? To conclude that the blood is not poisonous, from the fact that man lives with it diffused over all his organs, is simply nonsense. The only statement that we can permit ourselves to make, *a priori*, is that the blood is not sufficiently toxic for a quantity amounting to 1 kilogram to be able to kill or even seriously injure 13 kilograms of living matter. The toxicity of the blood is no doubt considerably below this estimate; but I have shown you by several experiments that this toxicity really exists, and I have fixed the somewhat narrow limits within which it is confined. I have been led to the conclusion that a kilogram of living blood contains in its plasma, and only in its plasma, enough poison to kill more than 1250 grams of living matter, and that a man would die toxæmic if his blood came to contain ten times as much poison as it does in its normal condition. But if the plasma of the blood is only slightly toxic, its cells contain poison, like all the cells of the body, and these toxic constituents of each cell can only be set at liberty by disassimilation or by the destruction of the cell itself. Among these substances there are some which are toxic. These poisons, which are contained in abundance in the cells of all the tissues, are of two kinds; there are organic substances resulting from disassimilation and secretion, and mineral substances, at the head of which we must place potass.

Among the products of secretion, bile, which flows periodically into the alimentary canal, contains poison; it derives its toxicity much more from its coloring matter than from the biliary salts. But, normally, the bile that is secreted is not very dangerous; its coloring matter and its salts are, for the most part, precipitated in the ålimentary canal.

The alimentary canal, however, is an important source of poisons; it contains, in addition to the potass supplied by various foods and the bile, the products of intestinal putrefaction. I had to take up this question of intoxication by putrid products from the points of view of many different experimentalists,—Gaspard, Panum, Hemmer, Bergmann and Schmiedeberg, Zülzer and Sonnenstein, Selmi, Gautier, Brouardel and Boutmy. Then I studied intestinal putrefaction; I showed that alkaloids exist in fæcal matter, that these alkaloidals are of several kinds, and that when those of one kind predominate in the intestines we also find them predominate in the urine. I established, according to Stich, the toxicity of fæcal matter. I analyzed the elements of this toxicity, and showed that it is due mainly to potass and ammonia, but that, when freed from these two elements, fæcal matter still retains a certain degree of toxicity which must not be overlooked. I have shown that intestinal antiseptic treatment, which causes the alkaloids to disappear from fæcal matter and urine, diminishes the toxicity of both.

Knowing the normal poisons and the various sources from which they spring, I was able to study a form of poison due to their retention, viz.: uræmia. But I took care to distinguish it from the nonpoisonous symptoms that arise in diseases of the kidneys,—albuminuria, hæmorrhage, cardiac and arterial injuries, and œdema, including cerebral œdema. Thus, as you know, I only admit as uræmic symptoms those that are toxic. I have, moreover, furnished the only convincing proof of the reality of toxic uræmia by showing that the urine of uræmic patients is not poisonous.

The urine of uræmic patients is not toxic, owing to the fact that all the poisonous substances normally eliminated by the urine are retained in the system of those suffering from this disease. But is all that is thus retained poisonous? If only a part is poisonous, which part is it? It is not urea. It is not the mass of extractive matter; it is not potass exclusively. The toxicity cannot be explained by any one of these bodies singly. Each of them contributes a different share to the general toxicity,—the coloring matter three-tenths, the extractive matter one- to two-tenths, and potass and other mineral substances four- to five-tenths. The knowledge of the multiplicity of the toxic agents enables us to understand, according to the one which predominates, the many clinical features that uræmic poisoning may assume, particularly the convulsive and the comatose forms. It explains the appearance of certain special symptoms, such as low temperature and pupillary contraction.

I think I have succeeded in showing you, gentlemen, that these pathogenic observations not only satisfy scientific curiosity, but that they have for corollaries practical applications; and that, in a word, they are far from being unimportant from a therapeutic point of view.

After having studied the form of intoxication resulting from the retention of the normal poisons, I commenced the study of the morbid conditions caused by the exaggeration of their formation,—for example, gastric disorders, constipation, and intestinal obstruction. I traced the history of various intoxications by poisons of intestinal origin, such as toxæmia from bad sausages; I quoted a case of Senator's, in which the cause of the malady was hydrosulphuric acid,—a case of poisoning from fish, which I observed personally, and in which the ill effects were attributable to the formation of an excessive quantity of alkaloids; I called your attention to a case of poisoning from some preserved goose, in which Brouardel and Boutmy discovered a poisonous alkaloid. I showed you that all these cases are, in reality, within the domain of infection before they end in intoxication. In all these cases, in short, we find, between the consumption of tainted food and the appearance of toxic symptoms, rather a long period of incubation. It seems to me that the poison elaborated by the microbes in the tainted food was too small in quantity to cause poisoning, but that the microbes, continuing to multiply with greater rapidity in the alimentary canal, amounted in a few hours to a prodigious number, and that then the toxic matter elaborated by them formed a mass of sufficient importance to produce poisoning. Here, again, incubation obliges us to admit infection; but the infectious agents form a poison, and the infection ends in poisoning. But the most common condition in which we find intoxication occurring through the excessive formation of poisons in the alimentary canal is, as I have told you, dilatation of the stomach, which, independently of the digestive and nervous troubles always recognized as being attendant upon the various forms of dyspepsia, seem to me to cause many other disorders. It engenders, especially, a habitually chronic albuminuria, which may become permanent, but which remains curable for a long time, and which is rapidly cured if, suspecting its cause, we take the trouble to seek it out, and if, having discovered it, we know how to contend against it. It is by provoking anomalous gastric fermentation, by rendering excessive intestinal fermentation, by preparing poisons, and especially acetic acid, that dilatation of the stomach vitiates the nutrition of the osseous tissue and produces a peculiar deformity of certain joints,—a kind of nodose rheumatism, osteomalacia, and, perhaps, rachitis. There are other diseases of degeneration which spring from disorders of the nutritive functions caused by dilatation of the stomach; I will merely mention those in which this pathogenic influence is most manifestly shown: chlorosis and pulmonary phthisis.

I showed the part played, even in infectious diseases, by certain secondary intoxications, and I was thus led to expound to you my views as to the treatment of typhoid fever, the cardinal points of which are, in my opinion, intestinal antiseptic treatment, general antiseptic treatment, antithermic treatment, —consisting of tepid baths, gradually cooled,—and a certain system of dietetics. I was thus enabled to formulate, with regard to typhoid fever, certain general rules that might be applied to other acute diseases.

I showed you the share contributed by poisoning in jaundice. This poisoning is twofold. The bile, contrary to what was supposed, is poisonous mainly in its coloring matter. What saves the system from the toxic power of this coloring matter is the urine, which is continually eliminating a portion of it; and also the cellular tissue and the fibrous tissues, the white fibers of which retain within themselves the excess of coloring matter that is not eliminated, and which, if it remained in circulation, would seriously affect the working of the nerve-cells. On the other hand, the biliary salts increase disassimilation, destroy muscle-cells and blood-corpuscles, and thus set free organic and mineral poisons, particularly potass.

Now, in many of the diseases that produce jaundice, the liver, whose normal function is to protect the system against the intestinal poisons, is diseased or checked in its working. It ceases to exercise its protective influence; it also ceases to form urea, and urea is the best diuretic. It is this substance which, by forcing the renal barrier, carries away the other toxic material. Thus, complete poisoning takes place, the successive phases of which are cholæmia, acholia, and uræmia. In fact, in jaundice, the true safeguard against poisoning is the kidney. As long as it acts, the patient's urine is very toxic; not owing to the bile which it contains, but from the matter produced by exaggerated disassimilation. If the kidneys perform their work of depuration insufficiently, the urine ceases to be toxic, but the patient is poisoned through the retention of the normal poisons.

We have seen that the normal poisons are not alone the cause of all intoxication. I showed you, in acute yellow atrophy of the liver, an example of anomalous substances produced by the vitiated elaboration of matter by the system. I allude to certain unusual albumins, to the unusual transformation of medicaments, such as naphthalin, which ceases in the case of atrophy of the liver to pass from the system in the form of naphthylsulphite of soda. Among these anomalous substances there are some which are toxic.

I will remind you that, in glycosuric patients, besides the symptoms arising from incomplete destruction of the sugar formed by the system, the latter may generate a substance which, in the urine of patients attacked with diabetic coma, takes a claret-colored tinge when brought into contact with perchloride of iron. This substance does not exist only in diabetic subjects; it has been found in dyspeptic coma, in certain cases of cancer of the stomach, pernicious anæmia, leucocythæmia, and I have observed it in dilatation of the stomach and in typhoid fever. It has been experimentally established, as you know, that this substance is toxic. Unlike the greater number of auto-intoxications that we have met with up to the present, what we call acetonæmia is self-poisoning by an anomalous poison,—a truly morbid one.

In cholera an anomalous elaboration of matter also exists, as shown by the violet coloration observed, even at the time of emission, in the urine of certain cholera patients that have been treated with naphthalin. But cholera is an example of complex poisoning. I told you that there exists in those attacked with cholera a primitive poison, the essence of which is unknown, which is produced either by the system under the influence of pathogenic microbes or by these microbes themselves. The existence of this poison is shown, in my opinion, by the special toxicity of the urine of cholera patients, which, on being injected into rabbits, produces in them the choleraic syndrome,—the appearance of cholera, but not cholera itself. But I also told you that, besides the symptoms caused by choleraic poisoning, those suffering from cholera underwent, at a certain stage of the disease, a secondary intoxication through the retention of the normal poisons, and I indicated myosis as the clinical criterion of the appearance of this uræmic poisoning.

I concluded the series of these lectures with therapeutic applications, with regard to intoxications in general, deduced from pathogenic knowledge. The treatment of self-poisoning derives several of its features from the antiseptic method. It was natural, therefore, to see what result might legitimately be expected from general antiseptic treatment.

In conclusion, I gave you certain reasons and quoted certain experiments, of a nature to lead us to hope that in the future general antiseptic treatment may produce good results.

And now, gentlemen, having taken a rapid retrospective glance at the ground we have gone over together, I think I am justified in making this assertion: When I have hazarded certain hypotheses, I have never disguised from you the fact that they were hypotheses; on the other hand, whenever I have made positive affirmations, they have been supported by experimental demonstration.

# APPENDIX.

## NATURAL DEFENSES OF THE ORGANISM AGAINST DISEASE AND INTERNAL SECRETIONS.

BY THOMAS OLIVER.

# APPENDIX.

## CHAPTER I.

### Natural Defenses of the Organism against Disease.

**New school of pathology: Charrin, Herter, Müller, and Brieger. Chemical defenses of the body. Bacteria and their products. Hæmolysines and bacteriolysines. Alkalinity of the blood an important defense. Metchnikoff and the Doctrine of Phagocytosis. Disease and individual idiosyncrasy. Internal secretions and Brown-Séquard. Thyroid gland. Reverdin, Kocher, and Horsley. Effects of thyroidectomy. Functions of thyroid gland. Baumann, Notkin, and Blum. Opotherapy and its limits. Enlargement of the spleen in fever and in blood conditions. Jawein's experiments: blood disintegration and splenic enlargement.**

In the preceding lectures on auto-intoxication Bouchard's main contention is that the human body forms poisons which but for the watchful activity of the eliminating organs, especially the kidneys, would injuriously react upon the body and endanger life. Although he discusses the subject of the entrance of poisons *ab extra,* he does not deal at any length with the question of how the body protects itself against the invasion of microbes. Since Bouchard's book was published a new school of pathologists has arisen. These men, working on different lines, have not only indicated how auto-intoxication may be prevented by the activity of the healthy emunctories, but have also shown how the body itself may be protected against disease by the operation of certain chemical and bio-chemical processes. Of recent writers who have given considerable attention to this question mention here need only be made of the work done by Charrin[1] and Herter,[2] also by Müller and Brieger. The subject, however, although still in its infancy, has not been ignored by Bouchard as his scattered writings show.

In an earlier section of this revised edition I have interposed fresh material in the text and have thus to some extent anticipated much that in the following pages may be said of those chemical defenses of the organism which are associated with the structure and activities of the cells that compose the tissues. Disease is a complex matter; sometimes due to the entrance of bacteria into the body or caused by the absorption of their toxins; it is against these that the human body projects such natural defenses as an alkalinity of the blood, acidity of the gastric juice and urine, acidity of the perspiration and of the vaginal secretion. When micro-organisms have entered the body the question naturally suggests itself: are the symptoms due to a mechanical disturbance caused by the presence of these microbes or do they depend upon the circulation of poisonous products formed by the minute organisms? Medical opinion rather leans toward the latter view. In some diseases—*e.g.*, diphtheria—the microbes are at first only upon the surface of a mucous membrane, and yet there are very marked constitutional symptoms. The injection of fluid cultures of bacteria from which the bacilli have been removed by filtration is also capable of causing disease. Without knowing exactly how, the serum of blood can destroy pathogenic bacteria. This power may depend upon the presence of proteids like enzymes since serum loses this property if it is exposed for more than an hour to a temperature of 56° C., while no loss of its antibacterial virtues is induced by simply drying the fluid. To the bactericidal substance present in serum Hankin has given the name of *alexin*. The substance itself is probably derived from leucocytes. It is no uncommon thing for the blood of one animal when injected into the veins of another of a different species to cause the colored blood-corpuscles of the receiving animal to undergo disintegration, and, should this occur to any considerable extent, there is usually hæmoglobinuria. The chemical substances that confer upon blood this globulicidal property are called *hæmolysins*. By some writers the term *bacteriolysins* is applied to those chemical compounds in blood-serum that destroy bacteria. While both of these protective substances are spoken of as *alexins*, it would be better to discard the term alexin altogether, since hæmolysins and bacteriolysins are of a more complex chemical nature than are alexins generally.

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[1] "Les Défenses Naturelles de l'Organisme," Paris, 1898.

[2] Herter, "Lectures on Chemical Pathology."

One other natural defense of the body claims attention, and that is what is known as phagocytosis or the destruction of bacteria by leucocytes, a doctrine first enunciated by Prof. Elie Metchnikoff, of the Pasteur Institute, Paris. Metchnikoff has shown that when the human body is refractory and is invaded at a particular locality by disease-bearing microbes, the bacterial toxins exert a chemical influence or chemiotaxis, whereby leucocytes are drawn to the part affected. There occur (1) a diapedesis of white corpuscles from the blood, and (2) phagocytosis in which warfare is waged between the microbes on the one hand, and the living cells on the other. In a refractory organism the polynuclear, nuclear corpuscles, or microphages, a type of leucocyte, kill the microbes and retire, leaving them to be taken up and digested by mononuclear corpuscles or macrophages, which are larger cells than those just mentioned. By this destruction of the microbes health is retained and disease averted. It is otherwise with the human body when it is run down or is in a receptive condition, for then the toxins exert a negative chemiotaxis; and as there is neither diapedesis nor phagocytosis, the microbes multiply, disease develops, and the infectious malady runs its course.

To the alkalinity of the blood must be ascribed some of the antibactericidal power which this fluid possesses since it has been found that this property varies with and is proportional to its alkalinity. The alkalinity of the blood is therefore a great defense. Increased acidity of the plasma weakens vital resistance and predisposes to disease. Certain morbid processes of themselves tend to increase this acidity. It is known, for example, that fever causes a diminished alkalinity of the plasma. Of the several sources from which the blood receives its acid constituents, we might mention food, gastro-intestinal fermentation, deranged metabolism giving rise to oxaluria and rheumatism; also disintegration of the nervous system followed by the presence of excess of phosphoric acid. The coma and stupor observed in the terminal stages of diabetes are generally admitted to be due to the presence of acid in the blood. The sodium carbonate, which is normally present in blood and which confers upon it a degree of alkalinity, is in diabetes neutralized by organic acids, particularly beta-oxybutyric acid. The sodium, thus freed from the carbonate, combines with the acid and is eliminated by the kidney, thereby removing, as Herter maintains, some of the harmful material. Similar combinations are probably formed with the ammonia of the blood, and, as a consequence, while there is a diminished excretion of urea, there is a rise in the total nitrogen of the ammonia elements from 2 to 5 per cent. in health to 25 per cent. in this malady. In dilated stomach, too, the absorption of organic acids from this viscus is followed by acidosis.

Into the subject of the agglutinating action of blood, or the power conferred in certain infectious diseases upon blood by toxins that have found their way thereto, whereby are brought about cessation of movement and a clumping together of the specific micro-organisms, as seen in Widal's reaction in typhoid fever, we cannot enter, nor can we deal with antitoxins, since these are beyond the scope of this book, and, besides the subject is still obscure. So far as antitoxins, however, concern us here, it is an interesting fact that where an animal has once been poisoned, either with pathogenic bacteria or with their products, there is conferred upon that animal an immunity to subsequent invasions of the micro-organisms which is due to the presence of specific products arising either out of the reaction of its leucocytes to the microbes, or they come from the bacteria alone and act by diminishing the receptivity of the organism and stimulating its natural powers of defense.

Some persons are known to be more susceptible to poisons than others. There is such a thing as individual idiosyncrasy. One person may suffer very readily and severely from the effects of a poison, while another scarcely suffers at all. This is seen in the action of morphine and alcohol; also in lead poisoning.[1] I am unable to offer any explanation of this individual peculiarity, but if the inquiry were pushed to its ultimatum the cause would be found to reside in the cells of the body.

It is only within recent years that the formation of an "internal secretion" by various glands of the body has come to be recognized, particularly of such glands as the pancreas, thyroid, and suprarenal. There may be several purposes served by such a secretion. Probably some of these secretions are protective. It would appear as if the thyroid gland destroyed substances that induce œdema, low temperature, and debility, etc. In order to bring about these accidents it is only necessary to extirpate the thyroid gland. After removal of the pancreas, for example, diabetes occur. It was Brown-Séquard who drew attention to the rejuvenating effects of testicular juice. The beneficial influences of internal secretions and of the interaction of glands are seen in the retardation of cancer of the breast by removal of the ovaries and by castration in the treatment of osteomalacia in the female. To Beatson, of Glasgow, we are indebted for much that we know of this subject.

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[1] "Lead Poisoning." Gulstonian Lectures delivered at Royal College of Physicians, London. Thomas Oliver, M.D.

For centuries the function of the thyroid gland was unknown. It was not until Reverdin and Kocher, of Switzerland, and Horsley, of London, extirpated the gland that we got to know something of its function, while as regards the therapeutic value of thyroid juice in the treatment of myxœdema my colleague, Dr. George Murray, of this city, can lay claim to having been one of the earliest pioneers. It was the two Swiss surgeons who showed not only that removal of the thyroid was followed by myxœdema, but that a peculiar condition was observed in children when the gland was congenitally defective. They also drew attention to the fact that when the gland is enlarged and too much thyroid juice enters the economy the processes of metabolism are hastened, palpitation is experienced, and there occur exophthalmos, muscular tremors, and slight rise of temperature. It is only recently, however, that some of these symptoms have come to be attributed to auto-intoxication. From the gland Notkin has removed two substances: *thyroproteid,* a genuine toxin; and *thyro-iodine,* from which two albuminous bodies can be obtained,—one a globulin and the other an enzyme. It is to the operation of thyro-iodine, or iodothyrin as it is sometimes called that Baumann attributes the special action of the thyroid gland, the gland itself forming this substance from iodine elements in the food. Notkin's thyro-proteid is toxic. When injected into animals it causes symptoms analogous to those observed in cachexia strumipriva. This substance represents the colloid material of the gland, and is considered to be, not a product of secretion, but an effete substance which the gland eliminates. After thyroidectomy it is this substance which, accumulating in the body, is believed to be the cause of the particular symptoms that follow ablation of the gland. In the normal state this material is destroyed or neutralized by the other element just spoken of as an enzyme and which is really secreted by the gland. Other bodies have been isolated, *e.g.*, a phospho-albuminated substance resembling the thyro-nucleo-albumin of Hammarsten. Morktonne holds the view that it is the function of the thyroid to collect the mucin contained in the blood and to transform it synthetically into nucleo-albumin in the gray cortical substance of the viscus. When the gland is extirpated this transformation ceases, mucin accumulates in different parts of the body and gives rise to myxœdema. Opinions are still divided as to the function of the thyroid gland, but, according to Charrin, it would appear as if it removed from the blood a phosphorated nucleo-albumin which has a slightly acid reaction; also that the gland secretes an alkaloidal leucomaine or thyro-antitoxin which neutralizes the nucleo-albumin just mentioned and forms with it a new substance necessary for the nutrition and development of the body. The thyroid gland would thus have a double function to perform: antitoxic and nutritive. The theories just enunciated all include removal of poisons from the blood. Bunge[1] is opposed to this teaching and he bases his opposition upon what he observed after incomplete removal of the gland. It is a well-known fact that if a small portion of the thyroid is left the usual symptoms that follow thyrotomy do not develop. Bunge's contention is that it is extremely unlikely the small portion left could remove from the blood what had hitherto been removed by the whole gland. His opinion, therefore, is that the thyroid gives off to the blood small quantities of a ferment that influences the metabolism of the body.

An account of the supposed functions of the thyroid gland would scarcely be complete in a book on auto-intoxication which failed to take notice of the ingenious theory enunciated by Dr. F.

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[1] "Physiological and Pathological Chemistry," Bunge.

Blum in *Virchow's Archiv,* 1901. To him the function of the thyroid gland is not so much to form an internal secretion which passes into the blood as to seize upon and render harmless certain toxic substances that are formed in the intestine and find their way into the circulation. Taking a certain number of dogs upon whom he had performed thyroidectomy, he fed some of them upon milk and others upon meat. Among the animals fed upon meat the mortality was as high as 96 per cent.; whereas, of the dogs fed upon milk or milk and bread, 40 per cent. survived the twentieth day after the operation. Eighty per cent. remained well as long as the milk diet was continued, but many of them died very quickly when meat was substituted for milk. It is not for a moment maintained that meat is in itself toxic and that it is rendered innocuous by the secretion of the thyroid gland. What is admitted is that certain toxins are formed in the intestinal canal by the operation of bacteria upon food and that meat favors their production, while the micro-organisms in milk rather suspend the development of the ordinary microbes usually met with in the alimentary canal. According to Blum, it is these bacterial toxins of intestinal origin, *enterotoxins,* that the thyroid gland seizes and destroys. When the thyroid gland is absent or diseased the absorbed toxins from the intestine produce changes in the body resembling myxœdema, viz.: tetany, cretinism, and other neuroses. On microscopical examination the kidneys of the dogs operated upon often exhibited the changes observed in interstitial nephritis. Blum, still further theorizing, states that the circulating *enterotoxins* are seized by the thyroid gland and converted by it into a fresh toxic substance containing iodine and named by him *thyreotoxalbumin,* a substance which is said to correspond more or less closely with the artificially isolated *iodothyrin.* To these experiments considerable clinical importance must be attached. They show, at any rate, that the production of toxins in the intestinal canal can be limited by a milk diet.

Several of the glands of the body are functionally interrelated, *e.g.,* the thyroid and pituitary, thyroid and ovary or testis. In cretins the testes are usually atrophied. Most physicians are familiar with the enlargement of the thyroid that occurs during pregnancy and often too at menstruation. In one of my own patients removal of the uterus and ovaries was followed within a few weeks by acute enlargement of the thyroid and marked exophthalmos, with tremor and palpitation of the heart.

It was Brown-Séquard[1] who first directed attention to the internal secretion of the testes. For much that we know of the function of the suprarenal bodies we are indebted to Schäfer and George Oliver. These glands according to Zucco, Supino, and Albanese, protect the economy against muscular poisons. They are supposed to remove worn-out pigments from the blood and either to store them up as chromogens or transform them so that they can be eliminated by the urine. When the adrenals are destroyed there is loss of muscular power and a sense of very great feebleness, as in Addison's disease. It is worth remembering from a therapeutic point of view that, while the injection of thyroid juice effects great improvement in myxœdematous patients, in those who are suffering from Addison's disease suprarenal extract is practically without influence. Opotherapy is therefore not without its limits, and experience has shown that it is not without its dangers, as witness the emaciation that follows the administration of thyroid juice. The removal of the suprarenal bodies even under careful antiseptic precautions is always a severe operation. Animals, as a rule, do not survive the operation well, although a dog experimented upon by Pol lived four and one-half months. Rats probably bear the operation best of all animals. The rich supply of nerve-fibers to the glands and the close connection of the latter with the sympathetic nervous system explain why it is that extirpation of the adrenals is borne so badly.

The pituitary body is often found to be enlarged after extirpation of the thyroid; also in sporadic cretinism and goiter. Iodine, too, is found in the pituitary. These facts suggest that the thyroid gland and pituitary body are somewhat interrelated in function. Disease of the pituitary body leads to malnutrition and to what is known as acromegaly.

The liver is one of the most important glands of the body, and has a distinct sentinel duty to perform. Healthy meat foods can become toxic when badly digested or imperfectly transformed. Grave uræmic symptoms develop in dogs in whom an Eck fistula has been made whereby the vena porta is made to pour its contents into the vena cava so that the blood coming from the intestine does not pass through the liver at all. So long as animals that have undergone this operation are nourished upon milk and bread they do well, but they become sleepy, convulsed, and comatose when fed upon meat. Nencki has shown that these symptoms are mostly due to the presence in the blood of carbamate of ammonia, the precursor of urea. This harmful carbamate can be got from the products of digestion of meat *in vitro* as well as from the stomach.

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[1] Comptes Rendus, vol. xliii, p. 422, 1856; vol. xlv, p. 1036, 1857.

It is unnecessary to deal with the functions of the other glands of the body. When the spleen, for example, is removed Laudenbach found that animals thus experimented upon became the subjects of a form of cachexia that in time proved fatal. For the blood to remain normal the spleen must be intact. Febrile processes are largely due to operations taking place in the parenchyma of this organ through the intensity of phagocytic action.

In acute infectious fevers and in certain forms of poisoning there is often found enlargement of the spleen. G. Dawein,[1] in trying to solve experimentally the problem as to why the spleen is enlarged in some fevers and not in others found, that if large doses of sodium and potassium chlorate were given to dogs the resulting splenic enlargement was directly proportional to the number of red corpuscles destroyed by the drugs. He found that a decrease of 1,000,000 erythrocytes in 1 cubic millimeter of blood corresponded to a spleen twice, and a decrease of 3,000,000 to a spleen five times, its normal size. In rabbits potassium chlorate does not cause disintegration of blood-cells, and therefore the spleen rather shrinks than enlarges. Splenic enlargement is therefore not due to any specific action of the drug upon the spleen or upon the splenic nerves. Toluylendiamin produces the same results by breaking up the red blood-cells. The splenic enlargement is due to the spleen harboring the broken-down blood-corpuscles. This functional activity is followed by hyperæmia and by hyperplasia. In order that the spleen shall enlarge the poison must cause disintegration of the blood-corpuscles. There must, in fact, be a rapidly progressing anæmia. The products of broken-down blood-corpuscles when seized upon by the cells of the splenic pulp probably have a stimulating influence upon the latter, and as a consequence hyperæmia and overgrowth occur. In chlorosis there is no enlargement of the spleen, because there is rather a deficiency in the formation of blood than destruction of it. When we remember that the splenic arteries communicate directly with the splenic pulp it is easy to understand how the cells have every opportunity of retaining and destroying abnormal or dead blood-corpuscles. If another example were required of the spleen being the grave of blood-corpuscles mention need only be made of the condition of this organ in leukæmia. This disease is no longer regarded as a primary affection of the spleen. The enlargement of the spleen in this malady is partly due to the fact that its pulp is often packed with dead leucocytes. Some cases of leukæmia are the result of an auto-intoxication that probably had an intestinal origin. In a few instances I have seen it follow typhoid fever, while in others there has been a history of some obscure form of intestinal illness.

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[1] **Virchow's Archiv, Bd. 161, ht. 3, p. 461.**

# CHAPTER II.

## AUTO-INTOXICATION OF INTESTINAL ORIGIN.

**Bouchard and auto-intoxication. Müller, of Marburg, and his limitations of the term auto-intoxication. Too exclusive a limitation. Hemmeter: auto-intoxication. Indicanuria. Estimation of indican in the urine. Albu and his classification of auto-intoxications. Micro-organisms in the alimentary canal: virulence of. Infection *versus* auto-intoxication. Stercoræmia: symptoms of. Stercoræmia in pregnancy, intestinal obstruction, and uræmia. The uncontrollable vomiting of pregnancy and auto-intoxication. Pinard, Bouffe de Saint Blaise, Dirmoser and Marcel Huge. Overfatigue and auto-intoxication. Views of A. v. Poehl and Verworn. Acid products in excess in the tissues. The "dyspeptic liver" and cirrhosis. Opinions of Boix and Rivoghi. Intestinal antisepsis. Views of authors pro and con.**

BACTERIOLOGY as an explanation of the cause of disease is in these days supplemented by the doctrine of poisons. Nearly all writers on this subject admit that it was Bouchard who gave the theory of auto-intoxication its proper position in medical literature. Prior to him, as Albu has pointed out, observations had been made in Germany, but it was the French physician who gathered together the data from which he wove his theory of auto-intoxication whereby he seeks to explain self-poisoning of man by metabolic products formed by the organism itself or by toxins produced within the gastro-intestinal canal. Deranged metabolism must alter the character of terminal organic products just as imperfect elimination leads to their accumulation within the body. Symptoms of poisoning, therefore, may be due either to overproduction or to retention of physiological or pathological products. Dr. F. Müller, of Marburg, prefers rigidly to limit the term auto-intoxication. He would not include the effect produced by poisons that have been introduced from the outside, nor the influence of toxins formed in the interior of the body by microbes, as in infectious fevers, but would restrict it to such conditions as carbonic acid poisoning and its slowly asphyxiating consequences; also uræmia, diabetic coma, and such pathological conditions as are due to imperfect thyroid and suprarenal gland activity. It is to be remembered that many of the poisons formed within the alimentary canal are products not of the organism itself, but of the microbes that inhabit the intestinal tract. Into the intestine there pass from many sources both harmless and harmful substances. The pancreas and liver, as well as the tubular glands of the mucous membrane, are constantly diverting into the alimentary canal numerous bodies, including ferments of all kinds, of which the economy tries to rid itself. The lining mucous membrane of the intestine is excretory as well as secretory, for if corrosive sublimate be injected into the vein of the ear of a rabbit the animal dies and at the autopsy there is found ulceration of the large intestine. Arsenic injected into the blood is in a similar, but in a less severe manner eliminated by the mucous membrane of the stomach. In the contents of the gastro-intestinal canal two disintegrating processes are at work: *fermentation* of the carbohydrates from decomposition and *putrefaction* consequent upon the breaking down of proteids, a process which is attended by the formation of substances that give off an extremely unpleasant odor.

We feel disposed to embrace within the term auto-intoxication more than Müller allows. In one form of auto-intoxication poisons are formed in the interior of the cells of the body as a result of metabolism: in another they are formed within the intestinal canal from decomposition or putrefaction of the food as a consequence of the operation of formed and unformed ferments, or they originate in a deranged chemistry of digestion which allows of the production of toxic bodies from ingested food. Hemmeter[1] doubts the reality of some of the hitherto accepted forms of auto-intoxication on the ground that the presence of chemical toxins has not been demonstrated in the blood of patients; also that if auto-intoxication is such a common thing people ought to become accustomed to the presence in the blood of these toxins just as they do to morphine and alcohol. He is of the opinion that the attacks come and go too abruptly to be due to poisoning; but it is this very fact that suggests the probability of their being toxæmic, since there must be in the intestine at times sudden evolutions of poison and almost just as quickly a rapid elimination of them. No one can watch a case of septicæmia without being struck by these facts, and, although septicæmia and auto-intoxication from an intestinal source are not exactly parallel conditions, and therefore comparable, yet there is in many respects a considerable similarity between these two forms of toxæmia. Hemmeter considers that many of the symptoms usually attributed to intestinal autotoxis are reflex in their nature. Müller is of the opinion, on the other hand, that one important cause in operation is hereditary predisposition. While not altogether discarding the theory, Hemmeter pleads for caution in accepting all that is attempted to be explained on the terms of auto-intoxication. One of the best criteria of the putrefaction of proteid food in the intestine is the presence of an increased amount of ethereal sulphates in the urine. The putrefactive products in the intestine vary with the microbes present. Sometimes the products formed are harmless amido-acids and phenols, at other times they are toxalbumins. In the human intestine under normal circumstances there are formed as a consequence of the putrefaction of proteid food such aromatic bodies as indol, skatol, and phenol. One portion of each of these bodies is eliminated in the fæces, while the other is reabsorbed and oxidized. Finally, in the liver the absorbed portion enters into sulphur combinations and is excreted by the kidneys combined with potassium salts, principally in the form of indoxyl-sulphate of potassium. While indican and the sulphur conjugated acids are present in small quantity in normal urine, they are sometimes found there in large quantities under pathological conditions. They are increased, for example, in intestinal obstruction, diarrhœa, typhoid fever, peritonitis, in internal abdominal suppuration, and in cancer of the stomach. Indicanuria has been found in lead and arsenical poisoning and in severe types of anæmia and chronic phthisis. A comparatively easy method of detecting indican in the urine is that recommended by Iaflé, viz.: fill one-half of a test tube with urine and add nearly the same quantity of hydrochloric acid, 2 to 3 cubic centimeters of chloroform, and a drop or two of liquor ferri perchloridi. Reverse the tube a few times. The chloroform separates out and is colored blue. On gently heating the tube a red reaction is obtained. The quantitative test for indican is a color one, but it is tedious to apply. The average quantity of indican in the urine of 24 hours is, according to Hoppe-Seyler, 0.17 gram to 0.27 gram. Since, however, it is in the liver that the putrefactive bodies already mentioned are converted into conjugated sulphur compounds we would naturally expect that in hepatic inadequacy these would be diminished in the urine. As a matter of fact, that occurs. The complex sulphur bodies have been found to be diminished in cirrhosis and in cancer of the liver.

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[1] "Diseases of the Intestines," vol. i, p. 335.

Albu[1] classifies auto-intoxications under four groups: (1) auto-intoxication caused by loss of function of an organ,—*e.g.*, myxœdema, pancreatic diabetes, Addison's disease, etc.; (2) auto-intoxication due to general abnormalities of metabolism,—*e.g.*, gout and oxaluria; (3) auto-intoxication from retention of physiological products of metabolism in the various organs, as witness the toxic phenomena observed after extensive burns of the skin; (4) auto-intoxication caused by overproduction of physiological and pathological products of the organisms,—*e.g.*, acetonuria and the coma of diabetes and cancer. Attention is drawn to Albu's classification only as a convenient mode of grouping together the phenomena of auto-intoxication, and not with any intention of adhering to it in these pages.

Of the diseased conditions that are generally attributed to abnormal decompositions occurring in the intestine mention need only be made of a few,—*e.g.*, gastro-intestinal catarrh, epilepsy, leukæmia, rickets, certain skin affections, chlorosis, etc. Taking any one of these maladies, what proof have we that such and such a disease is the result of intestinal decomposition or putrefaction? The ingestion of decomposing animal food, for example, may be followed by symptoms not unlike those observed in typhoid fever, ptomatropin poisoning, and gastro-enteritis. Quite apart from the character of the food taken, it is known that stagnation in the intestinal tract is followed by decomposition and putrefaction of the contents in a particular part of the alimentary canal. Wherever such a delay occurs micro-organisms flourish. Decomposition takes place in the stomach when this organ has become incapable of propelling its contents. Ileus and strangulation of the intestine produce similar results. The normal habitat of micro-organisms has only to be disturbed for serious consequences to follow. There are myriads of microbes normally in the mouth and gastro-intestinal tract of adult man. When these have their surroundings altered or when they pass into other places or organs it is then that they cause disease. Proof of this is seen in the operations of pneumococci. The bacterium coli, too, which is harmless when in the intestine, causes fatal peritonitis when it finds its way into the abdominal cavity, and pyelonephritis when in the urinary tract. It is not always easy to demonstrate the path by which microbes pass into the system from the intestinal canal. Nocard, Desonby, and Porcher[1] are of opinion that "during the absorption of food whole battalions of microbes pass from the intestine into the chyle and blood-vessels; that these are rendered harmless in the lungs and other organs and are, for the most part, eliminated by the urine." It is when the vitality of the tissues is reduced that microbes find conditions most favorable for their development. A healthy man can resist the action of microbes. It is when he gets run down in health that he becomes a prey to them. Neisser has shown that the chyle, blood, and internal organs of healthy animals can remain free from germs after the administration of food rich in microbes. The intestinal mucous membrane is not always a protective barrier. Virulent bacteria, for example, when introduced by the mouth can penetrate the intestinal wall, as is shown in meat poisoning and tuberculosis caused by contaminated milk. An unhealthy condition of the intestinal wall facilitates the passage of such microbes through it as the colon bacillus. In children who have died from acute gastro-enteritis the blood and internal organs have been found by Czerny and Heubner to contain bacteria that had evidently escaped from the intestinal canal. In strangulated hernia, too, bacteria have been found in the sac. Müller, while not accepting *in toto* the theory of auto-intoxication, considers such cases as those just mentioned to be rather of a contagious character and due to the entrance into the system of microbes from without; also that, even when the bacillus coli is found away from the intestinal tract, this microbe was probably introduced from without by means of food. He is of the opinion, too, that microbes when introduced from without are always more dangerous than those that have been for a period inhabiting the intestinal canal, since the individual under these circumstances ought to have developed an immunity to their products. It is sometimes extremely difficult to differentiate between infection and auto-intoxication. The greater the length of the period of incubation after exposure, the presence of enlargement of the spleen and feverishness, suggest infection; but it is well to remember that with certain classes of poisons there may be a period of incubation of one or two days before symptoms develop.

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[1] "Autointoxicationen des Intestinal Tractus," Berlin, 1895, S. 7.

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[1] Congress für Int. Medic., Wiesbaden, 1898, quoted from Müller.

Stercoræmia is a complex condition. The symptoms observed are vomiting, collapse; cold, clammy perspiration; small, rapid pulse; retention of the intelligence, and death from asthenia. It is not necessary that there should be intestinal obstruction to cause stercoræmia. While chronic constipation causing obstruction may induce it, stercoræmia may yet occur without this. It occasionally develops in persons whose kidneys are diseased, and may therefore be uræmic. I have also seen it occur and prove fatal in a case where after abdominal section the surgeon in closing the wound had inadvertently stitched a piece of intestine to the abdominal wall and where a fistulous opening subsequently formed. Here, although there was free escape for the intestinal contents, fatal poisoning still occurred either from absorption of toxins or from the passage of microbes through the injured wall of the intestine. Maci[1] brought before the Obstetrical Society of France (April, 1901) three cases of stercoræmia occurring during pregnancy. In one of the cases abortion in the second month of pregnancy seemed imminent: there were albuminuria and a rise of temperature, but the use of enemata, coupled with the administration of saline aperients was followed by the escape of hardened fæces, and thereafter the uterine hæmorrhage ceased, the temperature fell, and the pregnancy proceeded. In another of Maci's cases hyperemesis was very pronounced. By means of enemata and purgatives large fæcal masses were passed and pregnancy advanced. In a third case there were albuminuria and vomiting, with constipation of several days' duration. All of these symptoms ceased after the administration of rhubarb and benzo-naphthol. One feature present in Maci's patients was obstinate constipation. Budin, the French obstetrician, taught that constipation in pregnant women who are the subjects of albuminuria was often due to milk diet. Stercoræmia itself may be a cause of albuminuria, rise of temperature, and vomiting.

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[1] L'Obstrétrique, May 15, 1901, quoted in Supplem. to Brit. Med. Journal, Aug. 24, 1901.

Suppression of urine in uræmia is indirectly a cause of vomiting. It is difficult to say, when vomiting has continued for a length of time, whether the emesis of itself may not be the cause of the oliguria. The relation of cause and effect is not always quite clear. A short while ago I had under my care in the Newcastle-upon-Tyne Infirmary a man, aged 60, who for twenty-eight years had worked in a lead factory. His case was supposed to be one of lead colic at first, and subsequently of intestinal obstruction. He was extremely ill on admission, and during the few days he was in the surgical ward there was frequent vomiting, the material brought up being a thin, greenish-yellow liquid, strongly fæcal in odor. It was stated that the bowels had not been opened for eight days. The fæcal vomiting and history of constipation suggested intestinal obstruction, but there was no distension of the abdomen, and although patient was extremely thin no mass could be felt. The man, when first I saw him, looked very ill: his eyes were prominent and fixed; his heart's sounds were feeble, the pulse was small and there was a sense of air-hunger which, with no physical signs of disease in the chest, the deepest respirations did not seem to appease. The case presented all the characters of an auto-intoxication. Although enemata and salines brought away large quantities of fæcal matter patient was not relieved, for the stercoræmia continued. There was very marked oliguria from the first, followed by suppression. A catheter passed into the bladder drew off three or four teaspoonfuls of urine which on examination was found to be highly albuminous. On the third and fourth day after he entered the infirmary the man died, his symptoms of fæcal vomiting, etc., never having abated. At the autopsy the gastro-intestinal tract was found throughout to be quite healthy, but the kidneys were cystic and contracted and belonged to the type known as the small, granular kidney. How to explain the stercoræmia in this patient is rather difficult on any other lines than that in the early stages of the illness the vomiting was uræmic.

Since in previous pages I have more than once alluded to autotoxis in pregnancy, this is perhaps the proper place to draw attention, at greater length, to the mixed form of auto-intoxication that occurs during pregnancy and which is believed to be partly renal, hepatic, intestinal, and the consequence of altered metabolism. Women who are with child are often the subjects of digestive derangements of which *uncontrollable vomiting* is a most distressing and exhausting accompaniment. Morning sickness as a sign of pregnancy may occur at any stage, but the vomiting to which I wish particularly to refer is that severe form met with usually in the latter months of utero-gestation, not necessarily in the morning, but at any hour of the day, and which if not checked may lead to death. Numerous theories have been brought forward to explain it. Many physicians regard it as hysterical and therefore speak of it as a neurosis; others maintain that it is reflex in its causation and due to some abnormal development of the gravid uterus or to organic disease of the adnexa, while by an increasing number of observers it is believed to be a symptom of auto-intoxication. Since in some instances the vomiting of pregnancy is controlled by bromides, this circumstance suggests that it can be of purely nervous origin. How far it is due to heightened tension of the cervix (Copeman), retroversion or anteversion of the womb (Caseaux and Grailly Hewitt), ulceration of the "os" (Bennett), hyperæsthesia or rigidity of the internal "os," alternate rhythmic distension and contraction of the uterus, it is unnecessary to discuss. Here we are rather concerned with the possibility that in many pregnant women the vomiting is the expression of a toxæmia due to the absorption of poisons subsequently to be mentioned.

During pregnancy it is generally admitted that the blood becomes altered in composition, and that as effete matter is present in excess a burden is imposed upon the eliminating organs for its removal. The developing fœtus contributes its quota of waste material to the maternal blood, but that it is not the source of poisoning is shown by the occurrence of eclampsia in women who are the subjects of hydatidiform mole. Should, through any cause, an important emunctory fail to accomplish its proper amount of work, such nervous derangements as vomiting and convulsions are liable to arise. It is impossible, when these symptoms appear, always to name the particular eliminating organ that is at fault. Probably there is more than one. Albuminuria in a pregnant woman is regarded as a menace to health and as an indication of toxæmia. Pinard and Bouffe de Saint Blaise have drawn attention to the important part played by the liver and kidneys in auto-intoxication. They regard the vomiting of pregnancy as a sign of hepatic toxæmia and of similar significance to eclampsia, ptyalism, and other disorders. Dirmoser in 1897 expressed the opinion that the intractable vomiting of pregnancy is due to the absorption of such putrefactive products as indol and skatol. In analyzing the urine in 6 grave cases he found (1) urobilin, (2) the coloring matter of blood in 4 cases, (3) trace of albumin, (4) peptone in 4 cases, (5) acetone in 4 cases, (6) excess of oxalic acid, (7) excess of indol and skatol, and (8) hyaline and granular tube casts in 3 cases. Dirmoser therefore maintains that *(a)* metabolism is increased in all the patients; *(b)* that such abnormal bodies as albumin, urobilin, acetone, and peptone are found; *(c)* occasionally that acute nephritis is present. Just as it is not a single poison that is present so probably there is at fault more than one defective organ. Since the causes of the vomiting of pregnancy are therefore many, auto-intoxication probably plays a part, and that not the least important. The patient vomits because she is poisoned. Marcel Huge (*Gazette Hebdomadaire de Médecine*, etc., September, 1901) considers auto-intoxication to be the commonest cause of the vomiting of pregnancy. He holds that pregnancy, by overloading the blood, imposes burdens upon the emunctories; also that it impedes the functions of previously healthy organs by the pressure exercised by the gravid uterus or it may be that there is the development of some unusual form of toxins.

One other cause of auto-intoxication must be alluded to, and that is the overexcitement inseparable from the undue haste and the abnormal conditions of modern life. Alex. v. d. Poehl, of St. Petersburg,[1] has recently contributed a paper to the elucidation of this question which formed the subject of discussion by Professor Verworn at a meeting of German naturalists and medical men in 1901. Verworn draws a distinction between overexcitement of the nerves and their exhaustion. Independently of each other, these two physicians carried out a series of researches bearing upon the subject of overexcitement, mentally, bodily, and sexually. Verworn arrived at the conclusion that in consequence of overexertion there is induced a toxæmia to which excess of carbon dioxide in the tissues largely contributes. He explains the sense of exhaustion after laborious work on the theory of the available oxygen that is normally stored up in the nerve centers having been largely consumed. Poehl holds a similar opinion: he considers that there is diminished *tissue* or *internal* respiration due to altered nerve metabolism resulting from overexcitement. Urinary analysis strengthens this supposition. Overexertion reduces the alkalinity of the tissues. Not only does the urine become more acid, but the tissues themselves exhibit a similar chemical reaction owing to the accumulation therein of such products as lactic acid. Fatigue lowers the energy of the normal oxidation processes of the tissues. Whenever internal respiration is diminished lactic and other acids are not sufficiently oxidized; they accumulate and act both as local and general poisons. A sense of undue fatigue is removed by breathing fresh air and by draughts of alkaline mineral waters. To the causation of toxæmia consequent upon overexcitement such intermediary assimilation products as xanthin, hypoxanthin, and neurin, as well as lactic acid, in all probability contribute especially by the influence they exert upon the renal cells while being eliminated by the kidneys. So far as the question of overfatigue is concerned, nerve centers are more susceptible than are nerve trunks or nerve endings in muscle, for nerve centers have the more intense metabolism. Their freer vascular supply, while indicating that these centers are the seat of greater activity, is, on the other hand, a means whereby they are more exposed to the injurious influences of effete material that may be circulating in the blood.

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[1] Therapist, March, April, May, 1902.

However numerous may be the causes of auto-intoxication, there is not the least doubt that it is from the gastro-intestinal tract that the poisons are principally absorbed. The term auto-intoxication might be more appropriately applied to the production of poisons formed within the tissues and due to such a cause, for example, as that mentioned in the last paragraph, viz.: overfatigue, but for some reason or other, probably through Bouchard having mainly insisted upon the association, it has come to be more generally applied to constitutional states that are the outcome of a toxæmia caused by the absorption of gastro-intestinal products. The lassitude after a heavy meal, for example, is due, among other things, to the resorption of toxic peptones. Müller is opposed to this teaching, for he holds that the lassitude appears too early after the meal has been taken. Since it does not occur therefore when absorption is at its height he thinks it must be the result of mechanical overdistension of the stomach or the outcome of certain vasomotor influences. The symptoms, be it remembered, are less proportional to the amount of food taken than to its nature and composition. The liver is the organ through which most of the absorbed digested products pass. Sentinel-like, this organ refuses passage to some of these substances. If off its guard, some of them slip through that ought not. As a consequence of the prolonged action of abnormally prepared digested products upon the liver Bouchard and Hornot maintain that cirrhosis of this organ may develop. This so-called "dyspeptic liver" commences as a simple enlargement of the viscus. In patients from whom alcohol and syphilis can be excluded this dyspeptic liver may possibly be the origin of some of the hitherto unexplained forms of cirrhosis of that organ. Boix has witnessed in animals a simple enlargement of the liver become transformed into a veritable cirrhosis by the administration of butyric and acetic acid in the food. Rivoghi from his experiments concluded that indol, skatol, and phenol might possibly also induce cirrhosis. Out of 64 cases of cirrhosis of the liver he believed 4 to be due to dyspepsia. That the liver can become affected in acute intestinal disease and in intoxication is proved by phosphorus and sausage poisoning. The pathological changes in the liver are frequently the result of the action of toxins, for bacteria have been found in the organ. Deranged functional activity of the liver is sufficient to cause symptoms of toxæmia, especially if nitrogenous food is administered. Increased urinary toxicity almost invariably follows diminished antitoxic function of the liver. Bouchard names the quantity of urotoxies which an individual makes per kilo. This in health equals 0.464, the *urotoxic coefficient,* and he finds when the liver cells have become altered in structure that the urotoxic coefficient is higher than in the normal state. It may be doubled or tripled. Ammonia, potass, and extractive matters contribute to this hypertoxicity: ammonia itself is 40 times more toxic than urea. In the earlier part of this book Bouchard deals with the subject of the day and night variations of urinary toxicity: the toxicity of the day urine equals 31 urotoxies and that of the night 8. There is no need to reproduce here his arguments except to repeat that a day of muscular activity spent in the country in the fresh air diminishes by one-third the urinary toxicity—a diminution that is continued into the period of repose; also that after laborious exercise the urine often contains, if not immediately, then later on, more urea, more uric acid and other acid products as well as excess of chloride of sodium, whereas after brain work the urine is richer in sulphates and phosphates. Overfatigue, as already mentioned, adds acid substances to the blood and reduces the resistance of the human body to disease.

If, as Bouchard has demonstrated, the gastro-intestinal tract is the source of the largest number of poisons that cause autointoxication, then clearly this is the part of the body that calls for special attention and treatment. Prevention takes precedence of cure. Nitrogenous food is much more likely to induce autointoxication than will carbohydrates. The freer use of milk and the return to a simpler diet are called for since their use is followed by a reduction of ethereal sulphates in the urine. Constipation must be overcome by diet and by aperients. When these fail the administration of intestinal antiseptics becomes a necessity and medicines of this class, if they are to do any good, must possess little solubility and be therefore slowly absorbed so that they can traverse the length of the intestines. Müller is not a believer in intestinal antiseptics; he doubts their efficacy; he maintains that there is no proof that iodoform, naphthol, menthol, and the salicylic preparations diminish the quantity of ethereal sulphates in the urine or that these drugs influence intestinal putrefaction. My own experience is quite contrary to that of Müller. Again and again I have seen the most marked benefit follow the administration of intestinal antiseptics. In dilated stomach, where decomposition is often very great, antiseptics may do little good, but after all this is only a limited portion of the alimentary tract. The excessive acidity of the contents of the stomach has first to be neutralized. As the quantity of formed and unformed ferments in this viscus is too great to be readily influenced by antiseptics it becomes necessary to wash out the stomach perhaps on more than one occasion. I have never seen intestinal antiseptics do harm, but it is with these drugs, as with all synthetic preparations, there is a limit to their safety, as witness the effects of taking internally carbolic and salicylic acids in doses larger than medicinal.

Hemmeter,[1] although not a staunch supporter of the theory of gastro-intestinal intoxication, still considers that it is not without reasonable foundation: he has therefore in his book laid down four lines of treatment for intestinal auto-intoxication, viz.: prophylactic, dietetic, hydriatic,—*i.e.*, lavage,—and medicinal. In prophylaxis is included the avoidance of all food that is capable of undergoing fermentation and putrefaction. As there is an idiosyncrasy in some people to certain kinds of food experience must be the guide as to what is to be included in the dietary. Since albuminuria of a transitory character can be induced by the action of abnormally prepared digested products upon the kidney, a chemical examination of the urine should from time to time be made, for under treatment and simpler diet the albuminuria may quickly disappear and with it the severe headache and the accompanying sense of malaise. Lavage of the colon and anything that will promote the normal peristalsis of the intestine are of service. Hemmeter holds the view that in our efforts to combat intestinal auto-intoxication we may weaken by the administration of antiseptics the bactericidal powers which the normal intestine possesses. E. Vidal (*Revue de Chirurgie,* October 10, 1900) maintains that the secretion which is poured out from healthy intestinal mucous membrane possesses antitoxic properties, and that "in intestinal occlusion the fatal results are not exclusively due to the mechanical obstruction, but to a stercoræmic infection consequent upon loss of power of the intestinal wall to exert its antitoxic effect." R. Schütz (*Berliner klinische Wochenschrift,* 1900, No. 25) found that both castor-oil and calomel, under certain conditions, injured "the normal provisions for disinfection of the intestine." Experience, after all, must be our teacher. It is very improbable that the belief in the efficacy of calomel when carefully administered and in proper cases is likely to be shaken by the statements of opponents of intestinal disinfection, for improved peristalsis is one of the best means of ridding the system of toxic products. Calomel is too soluble a substance and it stays too short a period in the digestive canal to be an intestinal antiseptic in the ordinary sense of the word. Charrin found after administering 4 grams of naphthol-beta in twenty-four hours to three patients who were suffering from chronic enteritis that he had succeeded in suppressing one-third of their urinary toxicity. In hepatic disease Surmount similarly diminished urinary toxicity by one-half. It is the sparingly soluble intestinal antiseptics such as salol, thymol, and naphthalin that do good. The treatment of auto-intoxication by means of intestinal antiseptics is of little use without due attention being also paid to such prophylactic measures as careful dieting and the administration of suitable aperients.

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[1] "Diseases of Intestine," vol. i, p. 337, 1901.

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